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## The etiology of functional somatic symptoms in adolescents

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# Chapter 9

## General discussion

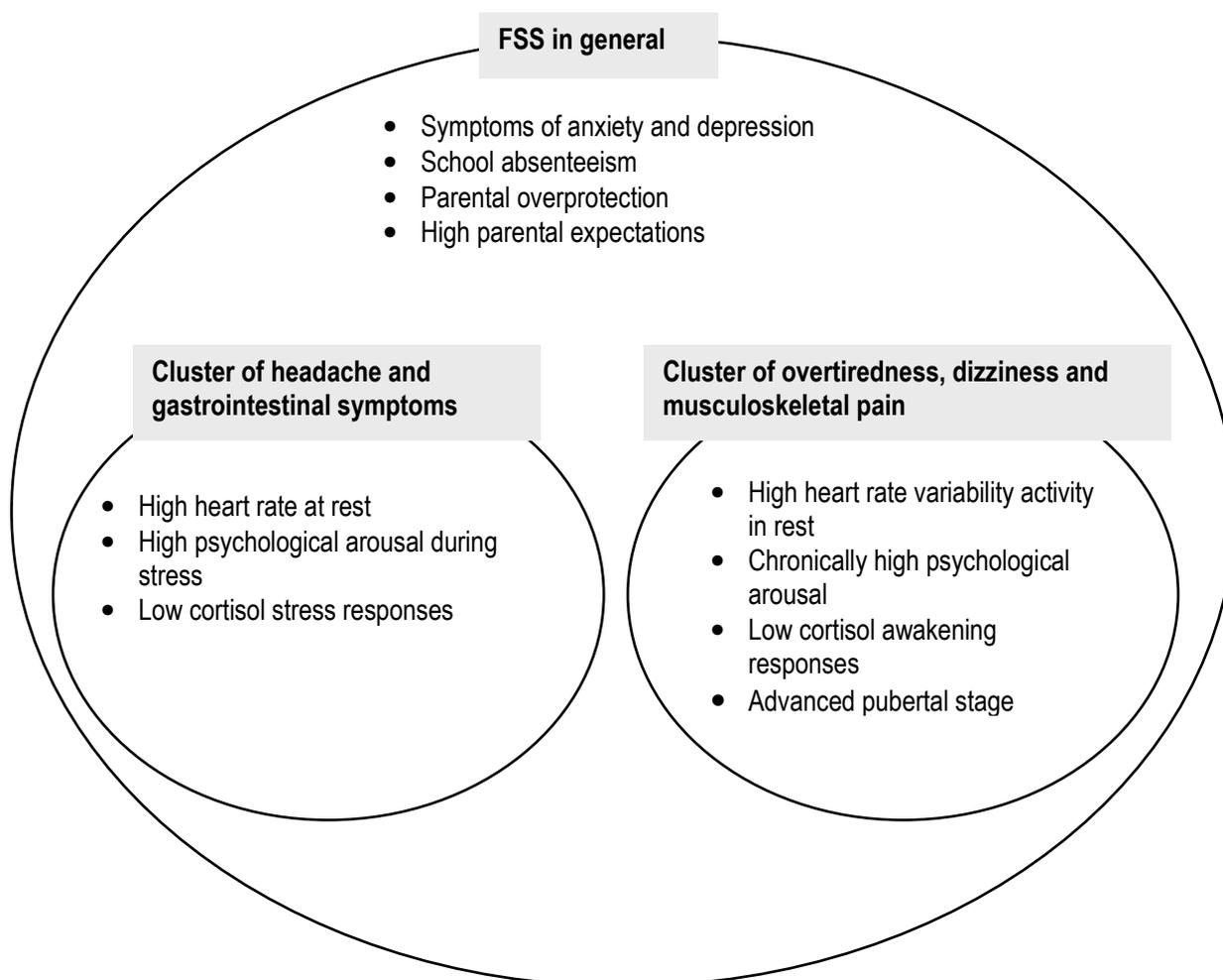
The aim of this thesis was to examine the role of biological, psychological, and environmental factors in the development and course of FSS in adolescents. Psychological and environmental factors were examined following a lumping approach, i.e. studying FSS in general, whereas biological factors were studied taking a splitting approach, i.e. studying specific FSS separately. The findings will now be put together, resulting in a new perspective on lumping and splitting FSS in adolescents.

### **An empirically based new perspective on lumping and splitting**

We performed a factor analysis to examine whether all items that were assessed with the Somatic Subscale of the Youth Self-Report (YSR) (Achenbach et al., 2003) loaded on the same factor. Two symptoms (eye problems and skin problems) had low factor loadings, suggesting they were not representative of the underlying construct, and were therefore not used. The remaining seven items (i.e., overtiredness, dizziness, headache, stomach pain, nausea, vomiting, and other pains) all loaded on one underlying factor, suggesting that these FSS reflected one underlying construct and could hence be lumped into a mean item score. Factor analyses indicate whether items can be lumped together or not, but do not inform about when it makes sense to lump items together. We decided to lump symptoms together when studying psychological and environmental factors, based upon the filter model developed by Rief and Barsky (Rief and Barsky, 2005). According to this model, two important bodily processes are involved in the development of FSS: bodily signal generation and bodily attention. Bodily signal generation is a constant process, but most bodily signals will remain unnoticed due to filter activity in the brain. This filter activity is likely decreased by bodily attention. In other words, the amount of bodily attention determines whether bodily signals are noticed or not (Rief and Barsky, 2005; Rief and Broadbent, 2007). Both an increased number of bodily signals and an increased amount of bodily attention have been found to play a role in the development of FSS (Rief and Barsky, 2005; Rief and Broadbent, 2007). The symptom-specific process of bodily symptom generation likely directly results from biological factors, while the more generic process of bodily attention is more likely to be influenced by psychosocial factors (Rief and Broadbent, 2007). This might explain why biological factors have been found to be involved in the specific background of particular symptoms, whereas psychological and environmental factors have been found to be generic risk factors (Hamilton et al., 2009; Moss-Morris and Spence, 2006). Therefore, FSS were lumped together when studying psychological and environmental factors and studied separately when examining biological factors. Our study on pubertal development showed that biological factors are indeed

symptom-specific: pubertal development predicted overtiredness, dizziness and musculoskeletal pain, but not headache and stomach pain in two large population-based cohorts of adolescents (Chapter 6). Headache and gastrointestinal symptoms may thus result from a different biological background than overtiredness, dizziness and musculoskeletal pain. Such a subdivision is also in line with a meta-analysis in adults, which showed that cortisol levels at rest are related to chronic fatigue syndrome and fibromyalgia, but not to irritable bowel syndrome (Tak et al., 2011). Thus, we performed another set of factor analyses to examine whether FSS could be divided into two symptom clusters. The advantage of studying two symptom-clusters instead of examining every particular FSS separately is that the use of clusters reduces the risk on chance findings, since it diminishes the amount of analyses that have to be performed. A confirmatory and an exploratory factor analysis supported the idea that, apart from a one-factor solution, a two-factor solution adequately fitted the symptom patterns. Headache and gastrointestinal symptoms loaded highest on the first factor, whereas overtiredness, dizziness and musculoskeletal pain loaded highest on the second factor (Chapter 7). Thus, the symptoms were divided into a cluster consisting of headache and gastrointestinal symptoms and a cluster of overtiredness, dizziness, and musculoskeletal pain, when studying cortisol levels and the autonomic nervous system. It is important to note that the factor analyses performed to identify a two-factor solution included musculoskeletal pain symptoms which were assessed with a different questionnaire than the YSR. The inclusion of musculoskeletal pain symptoms might have enhanced the division of FSS into two symptom clusters, since musculoskeletal pain symptoms were the symptoms that loaded highest on the second factor.

All in all, factor analyses indicated that both a one-factor solution and a two-factor solution fitted our data, and thus supported our belief that FSS partially share a common etiology, but that clusters of FSS also have their own specific etiologies. An overview of the investigated risk factors and their generic or specific associations with clusters of FSS is provided in Figure 1. First, we will discuss the psychological and environmental factors that were studied in relation to FSS in general. Then, we will deal with the investigated biological factors and their associations with the two different clusters of FSS.



**Figure 1. Model of generic and specific risk factors associated with FSS**

### **Psychological and environmental factors: the lumping approach**

Psychological and environmental risk factors and their associations with FSS were studied using multiple assessment waves. This had two major advantages. First, for the examination of psychological factors, both trait and state components of FSS could be studied. The trait component was the component that remained stable over the three assessment waves, and reflected unchanged risk factors for FSS (Duncan-Jones et al., 1990). The state component was the variance that was not accounted for by the trait component, and fluctuated over the assessment waves (Duncan-Jones et al., 1990). Anxiety and depression were also divided into a trait and state component. Modelling these trait and state components allowed a better reflection of the complex ways in which FSS were related to anxiety and depression. The state components of anxiety and depression had a strong effect on the state component of FSS measured at the same time, and the state component of FSS had a delayed and weaker effect on the state components of anxiety and depression. The trait components of anxiety, depression and FSS

were also strongly related to each other. These findings indicate that FSS and anxiety and depression not only have a mutual effect on each other, but also share a common background (Chapter 2). When studying intelligence, the variance of FSS was again divided into a state and trait component. Intelligence itself was not divided into a state and trait component, since intelligence is known to be quite stable over time (Waber et al., 2007). The trait component of FSS was significantly related to low intelligence, but only in adolescents whose parents had high expectations of their school performance, suggesting that it is not the low intelligence score itself but rather the overly high parental expectations that make adolescents with low intelligence scores at risk for FSS (Chapter 3). Another advantage of our longitudinal dataset was that it enabled us to study whether environmental factors perpetuated FSS in adolescents. Parental overprotection and school absenteeism were studied in this respect, and both appeared to perpetuate FSS (Chapters 4 and 5).

Why anxiety, depression, parental expectations, parental overprotection, and school absenteeism play a role in the development and course of FSS might be related to the before-mentioned process of bodily attention (Rief and Barsky, 2005; Rief and Broadbent, 2007). Most of these factors are likely to have increased the amount of attention adolescents pay to their symptoms. Anxiety and depression are known to make adolescents more self-focused (Bogels and Lamers, 2002). Overprotective parents may be more focused on their children's symptoms than nonoverprotective parents, and thereby increase the amount of attention adolescents pay to their symptoms. Further, the amount of attention adolescents pay to their symptoms likely increases by staying home from school, since at home adolescents are presumably less distracted from their complaints.

The advantages of lumping FSS together when examining psychological and environmental risk factors are that it increases the power to detect an effect and diminishes the risk of chance findings. The drawback of such an approach is that it precludes determining whether the risk factors are specific for particular clusters of FSS. To get a rough impression of whether psychological and environmental factors were differentially related to the two clusters of FSS used when studying the stress-axes, we performed cross-sectional regression analyses, in which the investigated psychological and social factors were entered one by one as predictors, with one of the two symptom clusters as the outcome variable, and gender and the other symptom cluster as co-variables (Table 1). All risk factors were related to both clusters except for intelligence, which was related to neither of the two. Anxiety and depression were about two-and-a-half times more strongly

related to overtiredness and dizziness than to headache and gastrointestinal symptoms, which suggests that psychological risk factors are more cluster-specific than environmental risk factors.

**Table 1. Univariate cross-sectional associations between psychological and environmental risk factors and two clusters of functional somatic symptoms.**

	Headache and gastrointestinal symptoms <sup>a</sup>	Overtiredness and dizziness <sup>a,b</sup>
Anxiety T1 (RCADS)	0.15 (<0.001)	0.37 (<0.001)
Depression T1 (YSR)	0.16 (<0.001)	0.43 (<0.001)
Intelligence T1 (WISC)	0.02 (0.49)	0.01 (0.83)
Parental overprotection T1 (EMBU) <sup>c</sup>	0.10 (<0.001)	0.17 (<0.001)
School absenteeism T2 (Teacher Report)	0.08 (0.01)	0.12 (<0.001)
School absenteeism T2 (Parent Report)	0.12 (<0.001)	0.08 (0.004)

*B* (*p*-value); <sup>a</sup>All associations are adjusted for gender and the other symptom-cluster;

<sup>b</sup>Musculoskeletal pain symptoms were not (extensively) assessed during the first assessment wave and therefore not included.

### Biological risk factors: the splitting approach

Biological factors were considered to be symptom-specific, since they likely influence the amount of bodily signal generation. The way in which biological factors can increase bodily signal generation will now be discussed. The first biological factor studied was pubertal development, which was thought to increase bodily signal generation by hormonal changes. Especially girls were expected to be at risk for developing FSS during pubertal development, since girls generally have more FSS than boys and this difference tends to increase during puberty (LeResche et al., 2005). However, we did not find evidence for such a gender difference, since pubertal development predicted the amount of overtiredness, dizziness and back pain in both boys and girls at follow-up (chapter 6). So, apparently not gender-specific sex hormones but rather a more general influence of pubertal maturation puts adolescents at risk for FSS. Another conclusion from this study is that pubertal development was related to overtiredness, dizziness and musculoskeletal pain, but not to headache and gastrointestinal symptoms. This suggests that pubertal development is a cluster-specific risk factor for FSS.

Dysfunctioning of the stress-axes is likely to play a role in the development of FSS as well (Tak and Rosmalen, 2010), because FSS have often been found to be the result of stressors (Gini and Pozzoli, 2009; Paras et al., 2009). The two most important stress-axes of the body are the hypothalamus pituitary adrenal (HPA)-axis and the autonomic nervous system (ANS). Cortisol levels after awakening and during social stress were used as indicators of the activity of the HPA-axis. Heart rate and heart rate variability before, during and after social stress were used as indicators of the activity of the ANS. As expected, the two FSS clusters were differentially related to these stress-axis indicators. The cluster of headache and gastrointestinal symptoms was related to low cortisol responses during stress and to high heart rate (reflecting autonomic hyperarousal) prior to a stressful situation. The cluster of overtiredness, dizziness and musculoskeletal pain was related to low cortisol responses after awakening and high heart rate variability (reflecting autonomic hypoarousal) prior to a stressful situation (Chapters 7 and 8). Both clusters were also studied in relation to psychological factors, namely psychological arousal before, during, and after a stressful situation. The cluster of headache and gastrointestinal symptoms was only related to high psychological arousal during a stressful situation, whereas the cluster of overtiredness, dizziness and musculoskeletal pain was associated with high psychological arousal before, during and after a stressful situation. Thus, the first cluster seemed more closely related to transient psychological distress and the latter to chronic psychological distress. Taking the findings on stress-axis functioning and psychological arousal together, the cluster of headache and gastrointestinal symptoms seems related to a maladaptive stress response, whereas the cluster of overtiredness, dizziness and musculoskeletal pain to an inability to recover from stressful situations.

### **Theoretical background: Selye's stress model**

The findings that the identified symptom clusters are differentially related to biological and psychological factors might be related to a stress model proposed by Selye back in the fifties of last century (Selye, 1950). This model states that an individual sequentially encounters three stages of stress in a stressful situation. During the first stage, known as the alarm reaction, a phase of low stress resistance is followed by a counter reaction, during which the individual's defence mechanism becomes active. This is the beginning of the second stage, the stage of stress resistance, in which maximum adaptation is obtained and, if everything goes well, a successful return to the equilibrium state of the body. If, however, the stressor continues or the stress defence mechanism does not work, the individual

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will move on to a third stage. In this third stage, the stage of exhaustion, adaptive mechanisms collapse. Our findings on stress-axis functioning suggest that the cluster of headache and gastrointestinal symptoms is related to a maladaptive stress response, and the cluster of overtiredness, dizziness and musculoskeletal pain to an inability to recover from stressful situations. Therefore, symptoms of headache and gastrointestinal symptoms might be more pronounced during the alarm stage, and symptoms of overtiredness, dizziness and musculoskeletal pain might be more pronounced during the final stage of exhaustion. Psychological risk factors like anxiety and depression may determine whether or not adolescents are capable of adapting to a stressful situation and thereby determine whether adolescents enter the stage of exhaustion (Litt, 1988). This might explain why psychological factors are more closely related to recovery-related symptoms than to stress-related symptoms. Another explanation might be that psychological distress is, like overtiredness, dizziness and musculoskeletal pain the consequence of an inability to recover from a stressful situation (Gourion, 2009).

The finding that autonomic hyperarousal prior to the stress test was related to the cluster of headache and gastrointestinal symptoms, and autonomic hypoarousal prior to the stress test to the cluster of overtiredness, dizziness and musculoskeletal pain might also reflect Selye's stress model. When experiencing a stressful situation, stress-axes initially react with hyperactivity. After they have been exposed to stress repeatedly, they might get exhausted, resulting in underactivity of the bodily stress systems. A meta-analysis in adults has indeed shown that recent stress is associated with high cortisol awakening levels, whereas chronic stress exposure is related to low levels (Miller et al., 2007). Another meta-analysis showed that high cortisol awakening responses are related to job stress, and low responses to exhaustion (Chida and Steptoe, 2009). Our findings with regard to the cortisol levels after awakening are in line with these meta-analyses: the cluster of overtiredness, dizziness and musculoskeletal pain was associated with low cortisol levels after awakening, while the cluster of headache and gastrointestinal symptoms showed a trend in the direction of high cortisol levels after awakening. The findings on cortisol levels during stress were not consistent with the theory of first hyper- and then hypoactivity of the stress-axes, since the cluster of headache and gastrointestinal symptoms was related to low and not high cortisol responses during stress. Moreover, the cluster of overtiredness, dizziness and musculoskeletal pain was not at all related to cortisol levels during stress. Thus, the theory seems to hold only for stress-axis functioning during rest (i.e. after awakening and prior to a stressful situation). This might be explained by the finding that HPA-axis functioning during rest and during

stress are only marginally related (Chapter 7). In fact, a recent study in TRAILS found that recent stress exposure is related to low and not high cortisol levels during stress (Bosch et al., *submitted*). This finding, thus, fits our theory that the cluster of headache and gastrointestinal symptoms, which was related to low cortisol levels during stress, is related to recent stress.

The environmental factors investigated in this study were found to exert a generic influence on FSS (Table 9.1). This is probably due to the fact that they mainly influence the amount of attention that was paid to symptoms, and only have an indirect influence on bodily signal generation. Environmental factors that are more directly involved in bodily signal generation, might be more cluster-specific. For example, transient stressors, like upcoming school exams, might be more closely related to the stress-related cluster of headache and gastrointestinal symptoms, whereas chronic stressors, like being bullied, might be more strongly related to the recovery-related cluster of overtiredness, dizziness and musculoskeletal pain.

### **Methodological strengths and limitations**

Some major strengths of this thesis helped to overcome problems with most previous studies on the etiology of FSS. The etiology of FSS was studied in a large population cohort, which increased the robustness and generalizability of the findings. Moreover, the TRAILS study, which was used for this thesis, was longitudinal and thus allowed us to use state and trait models and to draw conclusions about the direction of the effects of psychological and environmental variables. A final strength is that different FSS were examined, which enabled us to study whether risk factors could better be studied using a lumping or a splitting approach. This shed a new light on the etiology of FSS in adolescents. Apart from these strengths some limitations have to be acknowledged. First, the scale that was used to measure FSS, the Somatic Subscale of the YSR, only gave a rough estimate of the frequency and duration of the FSS (Achenbach et al., 2003). Adolescents reported whether they experienced the symptoms during the past six months, while choosing from only three answer categories (i.e. never, sometimes/a little bit, or often/ a lot). Future studies will benefit from a more extensive estimate of both the severity and the duration of the complaints, which will probably result in better estimates of the association between risk factors and FSS. More information about the pattern of occurrence of the symptoms will allow examination of whether symptoms that are transient are related to maladaptive stress responses, and symptoms that are chronic are related to an inability to recover from stressful situations. Second, the time lag between the assessment waves was about two to three years. Risk factors are likely to assert influence on

FSS in a shorter time frame than after two or three years. This might have led to an underestimation of the (longitudinal) effect risk factors had on the FSS. Third, a general population based cohort was used. Such a study design makes it easy to translate findings to the general population, but it also has a drawback. The number of adolescents suffering from severe FSS was only small. This might have lowered the associations found between risk factors and FSS. Fourth, studies on the stress-axes were cross-sectional, which precludes conclusions about causality. The dysfunctioning of the stress-axes could have been a consequence of the somatic symptoms instead of a risk factor. However, two longitudinal studies in adults have found that changes in stress-axis activity precede changes in somatic symptom level (Adam et al., 2006;McLean et al., 2005). A final limitation is that the functioning of the stress-axes was only assessed on single occasions (i.e. during the stress experiment or during awakening). Repeated assessments of stress-axis functioning would have given a more accurate estimate. However, we expect that the sample size of our population study would be large enough to compensate for random fluctuations in individual values.

### **Clinical relevance**

This thesis is more of theoretical than of practical relevance, since no conclusions about causality can be drawn from observational studies. Moreover, since the etiology of FSS was studied on a group level, results have unknown relevance in the doctor's office, where patient and doctor want to know the cause and most appropriate treatment of that particular patient's symptoms. Clinical intervention studies are needed to examine whether changes in risk factors truly diminish the amount of FSS adolescents experience and thus whether they are meaningful targets in the treatment of FSS. This thesis provides potential targets for these intervention studies. Moreover, some findings from this study might already be relevant for clinicians working with adolescents suffering from FSS. First, the common belief that FSS are the somatic manifestations of anxiety and depression was not supported by this thesis. We found, in line with previous research, that although anxiety and depression were closely related to FSS, they are not the same (Haug et al., 2004). In addition, we found that the association between biological factors and FSS was not the same as that for depression, since we found that FSS were related to low cortisol levels, whereas a recent meta-analysis in adolescents showed that depression is related to high cortisol levels (Lopez-Duran et al., 2009). Because we found that FSS are not the same as anxiety or depression, they presumably need to be treated differently. Second, FSS are likely to result from a multifactorial background, thus a broad treatment approach will probably be more helpful for adolescents suffering from FSS than a one-

dimensional approach. In particular the role of the parents should not be forgotten, since two of our studies showed, in line with previous research (Sanders et al., 1994), that parents can have a disadvantageous effect on the development and course of FSS in adolescents.

### **Applicability to adults and functional somatic disorders**

As mentioned in the introduction of this thesis, findings from studies on the etiology of FSS in adults cannot directly be extrapolated to adolescents. The opposite is true as well: findings from studies on the etiology of FSS in adolescents cannot plainly be generalized to adults. It would be interesting to examine whether the two symptom clusters identified in this thesis could also be identified in adults. The cluster of headache and gastrointestinal symptoms might be less prevalent in adults, since symptoms in adults are more likely to be chronic and are therefore more likely to be manifestations of exhaustion. This belief is supported by the findings that gastrointestinal symptoms and headache decreased, whereas overtiredness, dizziness and musculoskeletal pain increased during adolescence (Chapters 2 and 7). However, when taking functional somatic disorders (FSD) into account, another picture may emerge. FSD are not prevalent during adolescence, and were therefore not studied in this thesis (Gunn et al., 1993; Price et al., 1992; Sohrabi et al., 2010). Nevertheless, findings from the different symptom clusters might be generalized to FSD, since irritable bowel syndrome is likely to be related to the cluster of headache and gastrointestinal symptoms, and chronic fatigue syndrome and fibromyalgia to the cluster of overtiredness, dizziness and musculoskeletal pain. Our previous assumption that the cluster of headache and gastrointestinal symptoms is not prevalent during adolescence, is not reflected by the fact that irritable bowel syndrome is common in adults (Boekema et al., 2001; Quigley et al., 2006). Future studies are needed to examine whether adolescents who score high on headache and gastrointestinal symptoms are at increased risk for developing irritable bowel syndrome later in life, whereas adolescents with high scores on overtiredness, dizziness and musculoskeletal pain may be more likely to develop chronic fatigue syndrome or fibromyalgia. A comparison of our findings on symptom clusters and stress-axis functioning with findings on FSD and stress-axis functioning in adults suggests that the symptom-clusters and FSD are indeed related. The cluster of overtiredness, dizziness and musculoskeletal pain was, in keeping with findings on chronic fatigue syndrome and fibromyalgia (Tak et al., 2011), related to low cortisol levels after awakening. The cluster of headache and gastrointestinal symptoms was, in line with irritable bowel syndrome (Tak et al., 2011), not related to cortisol levels during awakening. We found ANS functioning to be symptom-

specific as well. However, a meta-analysis in adults did not find FSD-specific associations for heart rate variability (Tak et al., 2009). This might have been due to the low quality of most research conducted so far in adults (Tak et al., 2009). Studies of higher quality are necessary to find out whether irritable bowel syndrome is related to autonomic hyperarousal and fibromyalgia and overtiredness to autonomic hypoarousal.

### **Suggestions for future research**

As mentioned, this study is more of theoretical than of clinical importance. To draw conclusions about causality, intervention studies are needed. In addition, a new type of research design seems promising for examining the etiology of FSS in adolescents. This research method, which is called vector autoregressive modelling, tends to identify risk factors of FSS in a single individual by repeatedly assessing the association between risk factors and level of FSS (Molenaar and Campbell, 2009). The goal of such an analytic method is to provide participants feedback about which factors are aggravating their FSS. By implementing this knowledge in daily life, participants will presumably get better control of their symptoms. Another important aspect of future research should be that researchers from different disciplines join forces and examine the etiological background of FSS together, since this thesis supports previous findings that FSS result from a multifactorial background (Beck, 2008). Combining expertise from different disciplines is likely to lead to a better integration of research findings and thereby to a more complete understanding of the etiology of FSS (Farmer et al., 2010). Another type of research that looks promising for unravelling the etiology of FSS is fMRI research (Browning et al., 2011; Farmer et al., 2010). This research might be especially helpful to examine the processes of bodily signal generation and bodily attention. It might, for example, be interesting to investigate the symptom-specificity of the process of signal generation by studying whether adolescents who are suffering from particular symptoms are especially sensitive to stimuli applied to the bodily region where they are experiencing discomfort. The role of bodily attention is also worth studying while using fMRI, since during fMRI research the amount of attention can be manipulated. Using the same paradigm for studying patients suffering from different symptoms would enable researchers to examine whether bodily attention is indeed a generic process in the development of various FSS.

**Conclusion**

This thesis offers a new perspective on lumping and splitting in research on the etiology of FSS in adolescence. Environmental risk factors are most likely particularly involved in the amount of attention paid to symptoms, and thus can best be studied while lumping all symptoms together. Biological and psychological risk factors are more likely to play a direct role in the generation of FSS and can best be studied when splitting FSS into two symptom clusters. One of these symptom clusters is related to a maladaptive stress response and the other to difficulty to recover from stressful situations. Future studies are necessary to challenge this new theory, since, as Selye nicely stated, “many theories are of value simply because they encourage others to discover new facts that then lead to better theories”. Hopefully, this will also be the consequence of this thesis.

