From the Department of Clinical Neuroscience

KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

INTERNET-DELIVERED EXPOSURE-BASED COGNITIVE BEHAVIOR THERAPY FOR ADOLESCENTS WITH FUNCTIONAL ABDOMINAL PAIN DISORDERS

Marianne Bonnert

Karolinska Institutet

Internet-delivered Exposure-based Cognitive Behavior Therapy for Adolescents with Functional Abdominal Pain disorders
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Marianne Bonnert

Principal Supervisor:

PhD, associate professor

Brjánn Ljótsson

Karolinska Institutet

Department of Clinical Neuroscience

Division of Psychology

Co-supervisors:

PhD, MD

Ola Olén

Karolinska Institutet

Department of Medicine Solna

Clinical Epidemiology Unit

PhD, MD, associate professor

Eva Serlachius

Karolinska Institutet

Department of Clinical Neuroscience

Centre for Psychiatry Research

PhD, associate professor

Erik Hedman

Karolinska Institutet

Department of Clinical Neuroscience

Division of Psychology

Opponent:

PhD

Blake Dear

Macquarie University

Department of Psychology

Examination Board:

PhD, MD, associate professor

Mia Ramklint

Uppsala University

Department of Neuroscience

Division of Psychiatry

PhD, MD, associate professor

Robert Saalman

University of Gothenburg,

The Sahlgrenska Academy

Institute of Clinical Sciences

Department of Pediatrics

PhD, Professor

Örjan Sundin

Mid Sweden University

Department of Psychology

"After a while, if you are sufficiently bored or unemployed, you may want to read it from cover to cover."

— **Leonard Cohen**

ABSTRACT

Background: Irritable bowel syndrome (IBS), functional abdominal pain (FAP), and functional dyspepsia (FD) belong to the functional abdominal pain disorders, and are common in adolescents all over the world. Adolescents with IBS, FAP or FD often report anxiety, depression, school absenteeism, and a quality of life as low as children with inflammatory bowel diseases. The treatment effects from pharmacological or dietary treatments are unsatisfactory for this age group, while cognitive behavioral therapies (CBT) have shown some promising effects. However, CBT is rarely available as there are very few CBT-therapists trained in functional abdominal pain disorders. For adult IBS, exposure-based internet-delivered CBT (Internet-CBT) has been very successful, but this kind of treatment has neither been evaluated for adolescent IBS, nor adapted to the age group.

Aims: The overall aim of this thesis was to develop an effective and easily accessible treatment for adolescents with functional abdominal pain disorders. Specific aims were to investigate:

- The feasibility and potential efficacy of exposure-based Internet-CBT for adolescents with IBS, FAP or FD (Study I).
- The efficacy of exposure-based Internet-CBT for adolescents with IBS (Study II).
- Mechanisms of change in exposure-based Internet-CBT for adolescents with IBS (Study III).
- The feasibility and potential efficacy of a tailored exposure-based Internet-CBT for adolescents with FAP or FD (Study IV).

Methods: The feasibility and potential efficacy of the treatment were evaluated in an open pilot including adolescents (age 13-17) with IBS, FAP or FD (Study I). The efficacy of the treatment for adolescents with IBS was tested in a randomized controlled trial (RCT) with a wait-list control (Study II). Treatment mechanisms were investigated on data from the RCT, through analysis of change during treatment of two proposed mediators (perceived stress and avoidant behavior), and primary outcome (global gastrointestinal symptoms) (Study III). Lastly, the feasibility and potential efficacy of the treatment, when tailored specifically for functional abdominal pain and functional dyspepsia, were evaluated in an open pilot (Study IV). All trials had somatic symptoms as primary outcome, global gastrointestinal symptoms in Study I-III, and pain intensity in Study IV. Assessments were made at pretreatment,

posttreatment, and at 6-month follow-up (Study I-II and IV). In the RCT weekly assessments were included in the analyses (Study II). In Study IV, the follow-up assessments 6 months after treatment are still ongoing, and will therefore not be presented in the thesis.

Results: In the first pilot treatment adherence was high, and the improvements were significant and moderately sized, with a stable treatment effect after 6 months (Study I). The RCT showed significant improvement on all relevant outcomes in favor of the treatment with small to moderate effect sizes, which were stable or significantly improved 6 months after treatment conclusion (Study II). The analysis of mediators showed that reduction in avoidant behavior, but not reduction in perceived stress, predicted improvement in gastrointestinal symptoms due to treatment (Study III). The open pilot for FAP and FD showed significant improvement with strong effect sizes on all relevant outcomes, from pretreatment to posttreatment (Study IV).

Conclusion: Exposure-based Internet-CBT is a feasible and effective treatment for adolescent IBS. Feasibility and potential treatment effects may be increased with a tailored treatment for FAP and FD. Our results suggest that, it is by reducing avoidant behavior that gastrointestinal symptoms improve during exposure-based Internet-CBT, while a reduction in stress is not a necessary target in treatment.

LIST OF SCIENTIFIC PAPERS

I. Bonnert, M. Ljótsson, B. Hedman, E. Andersson, J. Arnell, H. Benninga, M. Simrén, M. Thulin, H. Thulin, U. Vigerland, S. Serlachius, E. Olén, O. Internet-delivered cognitive behavior therapy for adolescents with functional gastrointestinal disorders − an open trial. *Internet interventions.* 2014; 1(3): 141-148.

II. Bonnert, M. Olén, O. Lalouni, M. Benninga, M. Bottai, M. Engelbrektsson, J. Hedman, E. Lenhard, F. Simrén, M. Vigerland, S. Serlachius, E. Ljótsson, B. Internet-delivered cognitive behavior therapy for adolescents with irritable bowel syndrome: A randomized controlled trial. *American Journal of Gastroenterology.* 2016; Advance online publication, ahead of print.

III. Bonnert, M. Olén, O. Bjureberg, J, Lalouni, M. Hedman, E. Serlachius, E. Ljótsson, B. Reducing avoidant behavior improves gastrointestinal symptoms in adolescents with irritable bowel syndrome: An analysis of mediators in exposure-based cognitive behavior therapy. (Manuscript).

IV. Bonnert, M. Olén, O. Lalouni, M. Hedman, E. Särnholm, J. Serlachius, E. Ljótsson, B. Internet-delivered exposure-based cognitive behavior therapy for adolescents with functional abdominal pain or functional dyspepsia: A feasibility study. (Manuscript).

CONTENTS

LIST OF ABBREVIATIONS

FGID	Functional gastrointestinal disorders
IBS	Irritable bowel syndrome
FAP	Functional abdominal pain
FD	Functional dyspepsia
RAP	Recurrent abdominal pain
CBT	Cognitive behavior therapy
Internet-CBT	Internet-delivered cognitive behavior therapy
GI	Gastrointestinal
GSRS-IBS	Gastrointestinal symptom rating scale – irritable bowel syndrome
MLMM	Maximum likelihood mixed models
IBS-BRQ	Irritable bowel syndrome – behavioral responses questionnaire
PSS-10	Perceived stress scale – 10 items version

1 INTRODUCTION

About 90 % of all children that seek health-care for abdominal pain are deemed by their physician to have a functional gastrointestinal disorder (FGID) (1), that is, abdominal symptoms without somatic findings that explain the symptoms. Adolescents with FGIDs report a very low quality of life (2) and FGIDs in children and adolescents are associated with anxiety, depression and high school absenteeism (3). Symptoms from the abdomen are often unpleasant and cause much concern, as they could potentially be signs of serious illness. Hence, a variety of tests are often performed in the health-care to out-rule somatic causes (4). Moreover, this is a health-seeking population. In one study, adolescents with FGIDs used 20 times more health care than healthy controls (5). In the US, the estimated cost for hospital admissions for children with FGIDs during 2009 were over 11.5 billion US dollars (6). It has not been possible to determine a single cause for the symptoms (7), and most treatments have proven insufficient or unavailable for children and adolescents. The suffering that many adolescents with FGIDs report, together with the high health care consumption, are strong arguments for the need for an effective treatment. In the present thesis, I will describe the development and evaluation of a cognitive behavioral psychological treatment (CBT) for adolescents with FGIDs.

1.1 DIAGNOSTIC CRITERIA

As FGID is characterized by a clustering of symptoms, and a lack of reproducible anatomical or biochemical findings that fully explain the symptoms, there was a need for a standardized symptom-based diagnostic criteria to establish a diagnosis (8). A diagnosis enables a definition of the population, which in turn allows for evaluations of, and comparisons between, interventions targeting the symptoms. In 1958, Apley and Naish introduced the diagnosis Recurrent abdominal pain (RAP) for children and adolescents with abdominal pain (9), defined as three or more episodes of abdominal pain occurring over at least three months, that caused some impairment of function. In 1999, the Rome II-criteria introduced specific diagnostic criteria for the pain-predominant FGIDs in children and adolescents, such as irritable bowel syndrome (IBS), functional abdominal pain (FAP) and functional dyspepsia (FD) (10). In 2006, the Rome III criteria replaced Rome II and defined the pain-predominant FGIDs as symptom-based diagnoses with weekly abdominal pain or discomfort over the last 2 months not explained by somatic findings, located to the upper abdomen in FD, lower or middle abdomen in FAP, and related to a disturbed defecation pattern in IBS (11). In May

2016, the Rome Committee published new criteria, the Rome IV-criteria (12). All of the studies in the present thesis were conducted before that date, and are therefore based on the Rome III criteria.

1.2 PREVALENCE

FGIDs are common conditions all over the world as shown in prevalence studies from Europe, US, Australia, large parts of Asia and from South America (13). The changes in diagnostic criteria over the past 20 years have probably been one cause to the diversity in reported prevalence rates of FGIDs in children and adolescents, ranging from 12% to 29 % (14). A meta-analysis study, that pooled prevalence data from 58 studies, found a global prevalence of pediatric FGIDs of 13.5%, with IBS as the most frequent diagnosis (8.8%), while FD were reported to have a prevalence of 4.5%, and FAP (including functional abdominal pain syndrome) 4.4% (13). These figures are comparable to Swedish data on children and adolescents with FGID (15).

1.3 PROGNOSIS

Functional abdominal pain may persist over many years, also into adulthood (16). When 162 children (age 8-16) diagnosed with RAP were interviewed 9 years later, 41% had a current FGID, most commonly IBS (17.6%) (17). Another prospective study showed an increased risk for life-time or current anxiety disorders among young adults with a child-history of RAP, compared to healthy controls, as well as a heightened risk for life-time or current FGID (18). The risk for anxiety disorders was even more pronounced for those with a current FGID, with social anxiety and generalized anxiety disorder being the most prevalent diagnoses (18). Comorbid anxiety and abdominal pain have also been associated with higher functional impairment (19). In conclusion, following a natural course, many children and adolescents with FGIDs will fully recover, but for a large group the abdominal problems are persistent and often concurrent with anxiety disorders and functional impairment.

1.4   ETIOLOGY

The etiology of FGIDs is unclear, and the biopsychosocial model, first described by Engel (1977) is often used to explain the widths of factors shown to be associated with FGIDs (e.g., genetics, trauma, parental behavior, use of antibiotics, altered microflora, immune dysfunction/inflammation, life stress, diet, personality traits, coping strategies, social support) and how these factors act in concert to produce gastrointestinal (GI) symptoms (7). The broad acceptance of the biopsychosocial model for FGIDs offered the advantage of directing research towards including psychological and social variables (7), and away from an exclusively biomedical approach (20). However, the biopsychosocial model is too general to give any real guidance in treatment, and the vast amount of included variables may reflect the lack of knowledge about the causes, rather than the opposite.

A model that has received increasing support through experimental research is the bi-directional brain-gut model (20,21). The normal functioning of the brain-gut axis bidirectional communication is to continuously signal homeostatic information about the physiological condition of the body to the brain, and vice versa, signals that are usually completely imperceptible to the individual (22). However, numerous studies have shown changes in cortical modulation of pain and a heightened visceral sensitivity in adult IBS patients compared to healthy control (20). Dysfunction in the brain-gut axis communication might lower the threshold for visceral sensitivity, and allow physiological (non-noxious) stimuli to be detected by the individual. (20). This could explain how GI symptoms are exasperated in IBS and other FGIDs, and suggests a possible target for treatment.

1.5   PHARMACOLOGICAL, DIETARY AND PROBIOTIC TREATMENTS

There is a lack of trials evaluating pharmacological treatments for adolescents with FGIDs, hence the evidence for pharmacological treatment is weak (23,24). Anti-depressants are sometimes used in treatment of FGIDs in adolescents, but a recent Cochrane review concluded that the tricyclic anti-depressant Amitriptyline is the only anti-depressant that has been evaluated for FGIDs in the children and adolescents, and only in one high quality trial with no beneficial effects of Amitriptyline compared to placebo (25). Dietary changes are often suggested in outpatients clinics, but there are few trials published and thereby very little evidence for dietary interventions to be effective for pediatric FGID (26,27). The lack of effective pharmacological or dietary treatments has raised the interest for supplements with probiotics (live microorganisms). There is some support that the Lactobacillus LGG might

improve GI symptoms in children with IBS, but with few trials, the evidence for probiotics is still very limited (28). In summary, the evidence for pharmacological, dietary or probiotic treatments for pediatric FGID, is weak.

1.6   PSYCHOLOGICAL TREATMENTS

As the biopsychosocial model introduced psychological variables as important contributors to FGIDs, several psychological treatments trials have been conducted for adult IBS, a recent meta-analysis included 31 randomized controlled trials (29), whereas there have been considerably fewer studies conducted on psychological treatment for pediatric FGID, with eleven studies included in a recent review (27).

Hypnotherapy, that includes relaxation and ego-strengthening suggestions in order to change intestinal hyper-sensitivity and relieve stress (30), has been shown to be quite effective for pediatric IBS and FAP in one large study (31), with long-lasting effects even after five years (32). However, the interpretation of the results of this study are somewhat hampered by the use of one single therapist, which makes the distinction between therapist effect and effect from the treatment as such, difficult. Besides this study, there are two small studies conducted on hypnotherapy for FGID, with mixed results (33,34).

One randomized controlled trial used written self-disclosure as a treatment for RAP in adolescents, with some improvements after six months (35). In another trial a psychological treatment, described as "focusing on understanding and problem-solving", was combined with physiotherapy (36). The combined treatment were compared to physiotherapy alone, with no significant differences detected between groups (36).

In conclusion, the support for hypnotherapy as a treatment for pediatric FGIDs is limited, and the support for the other forms of psychological treatments, not including CBT, is almost non-existent.

1.6.1   Cognitive behavior therapy

CBT is the most evaluated psychological treatment for pediatric FGID (27,37). Cognitive behavior therapy for pediatric FGID has included relaxation and breathing techniques to relieve stress, coping strategies such as positive self-talk and distraction, and teaching parents

operant reinforcement to reduce pain behavior (38-40). In addition, some CBT protocols for abdominal pain also include exercises that target catastrophizing and negative thoughts (41-44), increased physical activity (42,45,46) and interventions directed toward sleep hygiene and diet (45,46). To summarize, prior CBT for pediatric FGID have targeted some of the exogenous factors suggested to contribute to GI symptoms in the biopsychosocial model, especially stress (47).

A Cochrane review on psychological treatments for pediatric FGID published in 2008 (48) concluded that CBT had promising effects, but that there was a need for larger and more-well designed studies. In 2010 Levy et al. published a large trial on 200 families that were randomized to either a 3-session CBT targeting parental behaviors, as well as teaching the children relaxation and coping skills, or a 3-session education about the GI systems anatomy and function, and information about diet guidelines (43). They reported three primary outcomes (pain intensity, global GI symptoms and functional disability) and saw a significantly larger improvement, as reported by the parents, in pain intensity and global GI symptoms immediately after treatment, in favor of CBT. However, the difference was not sustained at follow up. Furthermore, there was no difference between the groups on child-reported primary outcomes (43). Van der Veek et al. (44) compared six sessions of CBT with six meetings with a pediatric gastroenterologist, including 104 children and adolescents with FAP. The CBT consisted of one standard module (relaxation and breathing exercises), and 3 optional modules (targeting negative thought, maladaptive coping behavior and parents maladaptive coping) that the therapist selected. The pediatricians educated the family on the brain-gut axis, encouraged the child to continue normal activities despite symptoms, and prescribed medication. Both groups improved, with no significant difference between the groups (44). In summary, CBT showed promising effects in several early small studies with insufficient quality, but more recent large high-quality studies, have not confirmed the efficacy of CBT as a treatment for pediatric FGID. There are reasons to consider whether CBT for FGID could be enhanced.

1.6.2 Exposure-based cognitive behavior therapy

In adult IBS, exposure-based CBT has been very effective in improving global gastrointestinal symptoms, fear for symptoms and quality of life compared to wait-list control (49), a stress management intervention (50) and an intervention promoting behavioral activation without teaching exposure (51). The exposure-based CBT for IBS is partly based on the research demonstrating IBS-specific alterations in the brain-gut axis signaling.

Alterations such as, changes in pain modulation, and changes in brain regions associated with visceral sensations (21,52). These alterations may cause the IBS-patient to detect and experience more pain, and other symptoms from the GI tract (52). The term GI specific anxiety describes a pattern of fear and worry about GI symptoms (52), leading to behavioral avoidance of situations that might elicit symptoms (e.g. avoidance of food, certain social situations, or not having access to toilet facilities) (53). This pattern of behavioral avoidance has been associated with increased GI symptoms (54).

The fear and avoidance model of maintenance and exacerbation of GI symptoms is closely related to the established two-factor theory, or fear and avoidance model, for anxiety disorders (55,56), that has also been described for chronic pain (57). In accordance with this theory, it has been suggested that the internal stimuli of visceral sensations from the gastrointestinal tract in an IBS-patient have become conditioned stimuli associated with anxiety and pain (22). Exposure to GI symptoms is a mean to decondition the association that visceral stimuli must be harmful, and instead add new learning circuits associating GI symptoms with non-threats. This is the target in exposure-based CBT for IBS.

1.7 INTERNET-DELIVERED COGNITIVE BEHAVIOR THERAPY

Internet-delivered CBT (Internet-CBT) is similar to traditional CBT in many respects, but also has some distinct features that may enhance availability and reduce barriers to treatment (58). All treatment content is delivered over the internet via text-files, audio-files and videos. Thus, the treatment can be delivered over any geographic distances, and all treatment content can be downloaded and saved for later review and rehearsal, yielding an opportunity for deeper learning. Furthermore, there is no need for scheduled meetings, as the participant can take part in the treatment at any hour convenient. This means that parents and adolescents don't need to take time off from work or school to participate in the treatment. In addition, the therapist can deliver the treatment more effectively, as there is no need to go through all the content together with the participant. The therapist's role is to support by encouraging the participant's gradual progress in the treatment, as well as explaining and suggesting exercises when needed, all through text-messages sent through a dedicated web platform. Also, as all treatment content is delivered in the same mode and pace to all participants, the well-known risk of therapists drift is reduced (59). Consequently, Internet-CBT has the potential to be easily available, convenient and time-saving for both the participants and the therapists (58). Internet-CBT has been evaluated in over 100 trials for both psychiatric and somatic disorders

in adults with positive effects (60), as well as in children and adolescents with psychiatric or somatic disorders (58). Internet-CBT for adults has also shown promising results in terms of cost-effectiveness (61).

2 AIMS

The aim of the thesis was to develop an effective and easily accessible treatment for adolescents with functional abdominal pain disorders. Specific aims for each study are presented below:

2.1 STUDY I

The aim of the first study was to evaluate the feasibility and potential efficacy for exposure-based Internet-CBT for adolescents with IBS, FAP or FD. The hypothesis was that the treatment would be feasible and improve gastrointestinal symptoms and secondary outcomes, such as pain interference and fear of symptoms.

2.2 STUDY II

The aim of the second study was to evaluate the efficacy for exposure-based Internet-CBT for adolescents with IBS, compared to a wait-list control. The hypothesis was that Internet-CBT would lead to larger improvement than wait-list control in gastrointestinal symptoms, as well as secondary outcomes such as quality of life, avoidant behavior and fear of symptoms.

2.3 STUDY III

The aim of the third study was to investigate mechanisms of change in exposure-based Internet-CBT for adolescents with IBS, using data from Study II. The hypothesis was that Internet-CBT, targeting the mechanism of GI-specific anxiety, would lead to improvement in gastrointestinal symptoms through a prior reduction in avoidant behavior.

2.4 STUDY IV

The aim of the fourth study was to evaluate the feasibility and potential efficacy of an exposure-based Internet-CBT tailored for adolescents with FAP or FD. The hypothesis was that the credibility, adherence and satisfaction with treatment would be high, and that the treatment would lead to at least moderate improvements in pain intensity, as well as

secondary outcomes such as global gastrointestinal symptoms, quality of life, avoidant behavior and fear of symptoms.

3 METHODS

3.1 DESIGN, ASSESSMENTS AND STATISTICS

Study I was an open pilot without control group, including 29 participants who received Internet-CBT. Primary outcome was the global gastrointestinal symptoms measured with the adolescent-reported Gastrointestinal Symptoms Rating Scale (GSRS-IBS) (62). Assessments were made online at pretreatment, posttreatment and 6 months after treatment conclusion. Data were analyzed with dependent t-test, to estimate significance changes from pre- to posttreatment, and from pretreatment to 6-month follow up. Effect sizes were calculated with Cohen´s *d*, that is the standardized mean difference, with the limits for meaningful effects suggested as *d*=0.2 (small), *d*=0.5 (moderate) and *d*=0.8 (large) (63) , see Figure 1 for illustration of the effect sizes.

Cohen's d effect size - standardized mean differences

| *d* = 0.2 | *d* = 0.5 | *d* = 0.8 |
| Small effect size | Moderate effect size | Large effect size |
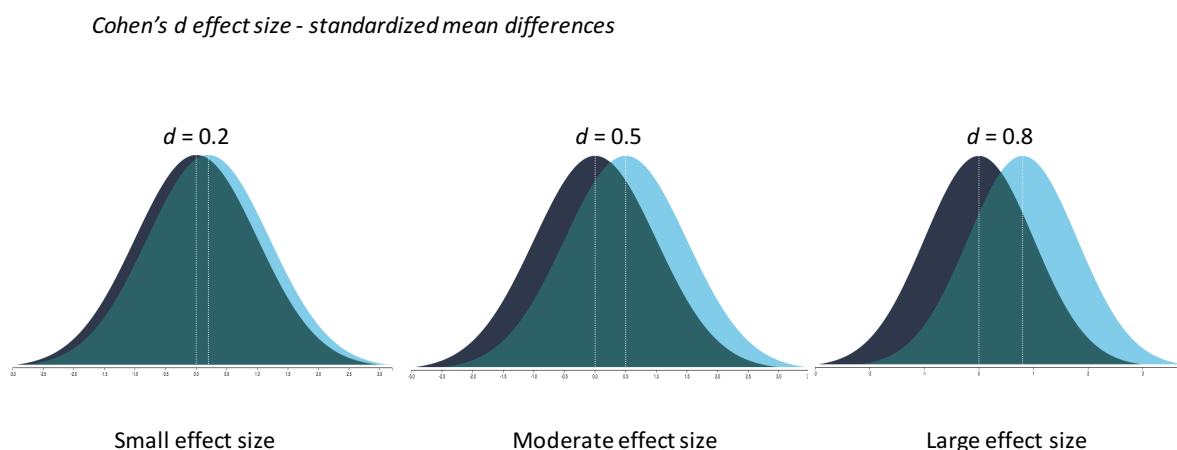
Illustrations from rpsychologist.com

Figure 1. Illustration of Cohen's *d* effect-sizes

Study II was a randomized controlled trial using wait-list as control, with 101 adolescents included, among them 47 received Internet-CBT while 54 were randomized to the wait-list.

Primary outcome was the GSRS-IBS. Assessments were made on-line pretreatment, weekly during treatment, posttreatment, and for the treatment group also at 6-month follow up after treatment conclusion. Participants on the wait-list received the treatment after posttreatment assessment had been completed. Analyses were conducted on intent-to-treat basis with restricted maximum likelihood mixed models (MLMM) to estimate if there was a significant time*group interaction effect on change from pretreatment to posttreatment. Effect sizes were calculated with Cohen's *d*. Parent-rated measures were clustered on the adolescent, since both parents provided data when possible. To estimate the change within the treatment-group, from pretreatment to follow-up, the MLMM were used with separate slopes from pretreatment to posttreatment, and from posttreatment to follow up, that were summed when investigating change from pretreatment to follow-up.

Study III was a mediation analysis using data from the randomized controlled trial in Study II. Proposed mediators were avoidant behavior measured with the irritable bowel syndrome behavioral response questionnaire (IBS-BRQ) (54), and perceived stress measured with the Perceived Stress Scale (PSS-10)(64). The outcome was the GSRS-IBS, and the independent variable was change over time as a function of group. Assessments were made online pretreatment, posttreatment, and weekly during treatment on both mediators and outcome. Mediation was estimated with MLMM analyses estimating the paths connecting three variables, the *X* (independent variable), *M* (mediator variable), and *Y* (outcome variable). The X-Y path estimated the effect of group on the outcome, the X-M path estimated the effect of group on the mediators, while the M-Y path estimated the effect of the mediators on the outcome (65). The total mediated effect is calculated as the product of the estimates of the X-M path and the M-Y path (66). See Figure 2 for illustration. Time-lagged analysis was made to confirm unidirectionality, that is, that the mediator changes before the outcome, and not as a consequence of a prior decrease in the outcome.
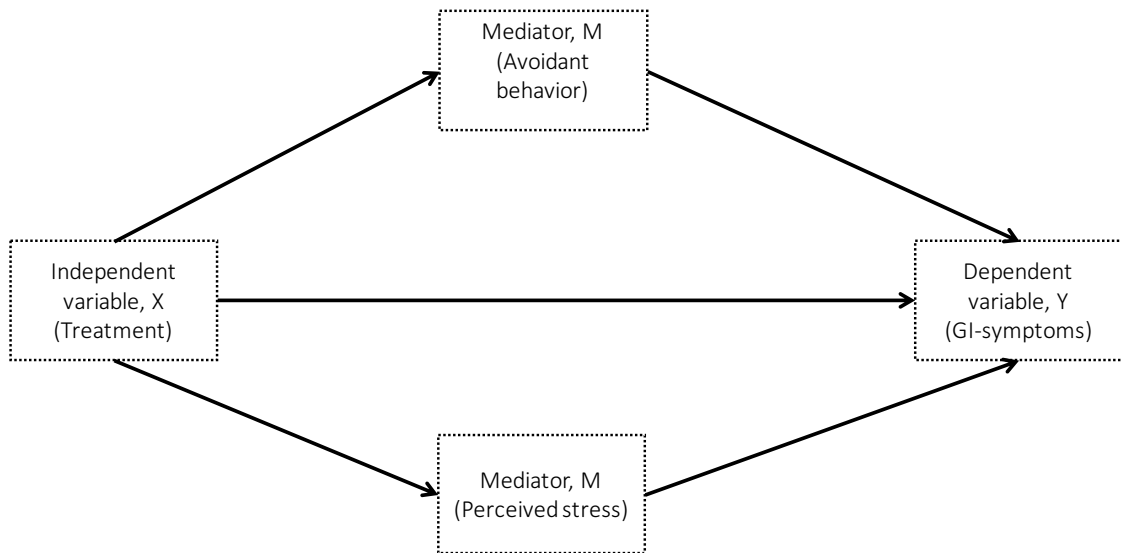
Figure 2. Mediational paths

Study IV was an open pilot without control group (n=31), where all participants received the Internet-CBT. Assessments were made online at pretreatment and posttreatment. Treatment credibility and working alliance with the therapists were assessed at week 2 and week 4 during treatment, respectively. Feasibility criteria were acceptable treatment adherence, acceptable treatment credibility, good working alliance with the therapist, satisfaction with the treatment, and potential efficacy. Primary outcome for potential efficacy was pain intensity as reported by the adolescents, measured with Faces pain rating scale-revised (67). Outcome data were analyzed using the dependent Student's t-test and effect sizes were calculated with Cohen's *d*.

3.2   PARTICIPANTS

All participants in Study I-IV were 13-17 years old, had been assessed by a physician to have a functional abdominal disorder, had one parent who was willing to participate in the treatment and had access to a computer and internet on a daily basis. In Study I all participants were living in Stockholm, were recruited through their treating physician, and had IBS (n=19), FAP (n=5) or FD (n=5). Studies II and IV included participants from all of Sweden. Advertising in national media and mail-lists to pediatricians were used to spread information about Study II, while only pediatricians were informed about Study I and IV. In

Study II all included participants had IBS. In Study IV all participants had FAP (n=25) or FD (n=6). There were more girls than boys in all studies (62-76% girls), and the mean age was 15 to 15.5 years. Duration of symptoms was four to five years. There were considerably more mothers than fathers who were the active parent in the treatment in all studies (72-90% mothers).

3.3 THE TREATMENT

The Internet-CBT protocols used in Study I-II and IV had the following common features, described below.

The treatment was an adapted version of the exposure-based Internet-CBT for adults with IBS (49). The main target in treatment was exposure for abdominal symptoms by reducing avoidance and provoking symptoms. For instance, the participants were encouraged to eat food that they avoided for fear of symptoms (e.g. dairy-products), or take the bus to school instead of letting parents drive them to avoid stressful situations that could elicit symptoms, or to remain in school throughout the school day regardless of symptom level. Participants were encouraged to gradually increase the difficulty by combining multiple challenges, such as first drink large amounts of milk, then take the bus to school and stay there all day.

The parents were mainly taught to reduce their attention to the adolescent's symptoms, in order to reduce the risk for reinforcement of the adolescent's symptom behavior, and to support their child to complete the treatment and carry out exposure exercises. Parents were also encouraged to routinely spend positive time with their adolescent in order to increase the focus on healthy behaviors, and promote a positive relationship to better be able to support their child in treatment.

The treatment content was delivered in weekly modules and contained texts about how symptoms are maintained through the brain-gut signaling and how behavior and exposure to symptoms can affect the signals, supported by videos, audio-files and examples. In each module the participants answered questions about their own symptoms and behaviors related to the content of the module, and what exercises they planned to do during the week. The next module began with a follow-up of the previous week's exercises. The modules were unlocked sequentially as participants worked their way through the treatment.

All treatment content was delivered over the internet. The adolescent and one parent were active in treatment while both parents were encouraged to take part in the content of the

parent treatment. The adolescent and the parent had separate login credentials. They received weekly therapist support from a clinical psychologist over the whole treatment course, through written messages within the platform. Therapist support consisted primarily of encouragement of any progress made in the treatment and support to find individual exposure exercises. The therapist also reminded participants to log in if they lagged behind, through platform-delivered mobile text-messages and through phone-calls.

3.3.1 The Internet-CBT in Study I for adolescents with FGID

In Study I we included adolescents with IBS, FAP and FD. They all received the same treatment, which consisted of 6 modules over 8 weeks, and the parents had 4 modules over the same time period. In this treatment the adolescents were taught mindfulness and acceptance exercises, in order to decrease reactivity caused by abdominal symptoms. The adolescents were also taught how to change problematic behavior around toilet-visits (i.e., frequent, urgent or prolonged visits), a common problem in the IBS-population. Those who did not have these kinds of behaviors were instructed to skip the exercises related to toilet behavior. Exposure-exercises were planned and conducted from module 4 to module 6. Modules 5 and 6 in the treatment were bi-weekly, to provide enough space in time for exposure exercises.

3.3.2 The Internet-CBT in Study II for adolescents with IBS

In Study II, to which only adolescents with IBS were included, the Internet-CBT was prolonged to ten weekly modules (during ten weeks) for the adolescents and five bi-weekly modules during 10 weeks for the parents. In the first modules (1-3) the adolescents mapped their IBS-specific behaviors in detail, were taught functional analysis, conducted a behavior experiment and planned exercises to reduce problematic toilet behavior. Exposure exercises were planned and executed from module 4 to module 10. The parents were taught basic positive parenting skills, in order to support their child to do the treatment. The parents could follow their child's treatment through downloadable PDFs containing the text in the weekly module. For an overview of the treatment, see Figure 3.
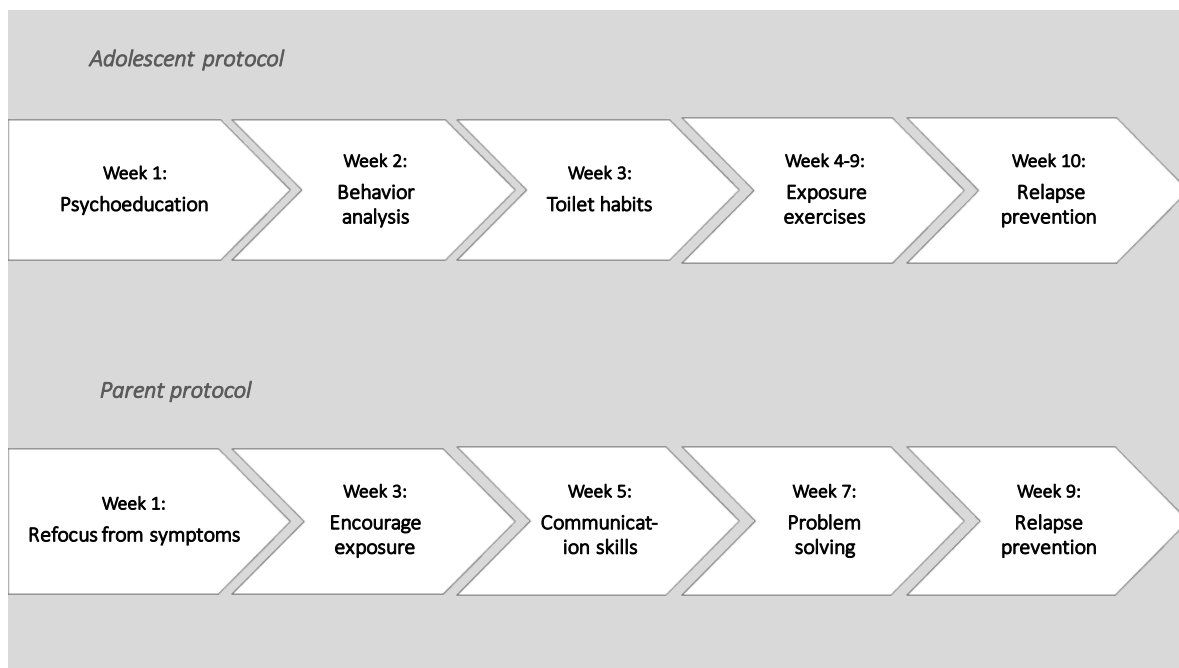
Adolescent protocol

| Week 1: Psychoeducation | Week 2: Behavior analysis | Week 3: Toilet habits | Week 4-9: Exposure exercises | Week 10: Relapse prevention |

Parent protocol

| Week 1: Refocus from symptoms | Week 3: Encourage exposure | Week 5: Communication skills | Week 7: Problem solving | Week 9: Relapse prevention |

Figure 3. The Internet-CBT in Study II

3.3.3 The Internet-CBT in Study IV for adolescents with FAP or FD.

To Study IV, the ten weeks long Internet-CBT used in Study II was further adapted. All examples involving IBS-specific behavior (i.e., behaviors related to the symptoms of defecation problems) were exchanged for examples better describing FAP or FD (i.e., behaviors related to abdominal pain, early satiety or nausea). All toilet behavior exercises were removed, and an exercise teaching neutral verbal labeling of symptoms (i.e., sensations, thoughts and feelings about symptoms) was added. The exposure exercises were planned and conducted during week 4 to week 10, as in Study II. The parents mapped own behavior when responding to their child's symptoms and were encouraged to decrease behavior that could risk perpetuating abdominal symptoms.

3.4 ETHICAL CONSIDERATIONS

The rigorous recruitment procedure in the studies ensured that included participants had a functional abdominal pain diagnoses, and that a somatic cause for the abdominal problems was ruled out, as all participants in Study II and IV had the same basic medical investigation confirmed by a signed health-form from the treating physician. Other serious psychiatric or psychosocial conditions that required immediate intervention were ruled out before inclusion

through an on-line screening procedure as well as a clinical intake interview with a psychologist. The adolescents and parents (all legal guardians) signed an informed consent before inclusion, and the adolescents were specifically informed that they had the right to discontinue participation in the study whenever they wished, without having to specify a reason.

The web-based platforms used for assessments and treatment were specifically developed for the purpose and used a double authentication procedure to login. All studies were approved by the Regional Ethics Review Board in Stockholm, Sweden

4 RESULTS

4.1 STUDY I

The primary outcome, global gastrointestinal symptoms, showed a significant improvement from pretreatment to posttreatment (mean difference -6.48; 95% CI [2.37, 10.58]) and from baseline to follow-up (mean difference -7.82; 95% CI [3.43, 12.21]). The effect size was moderate (within-group Cohen's d = 0.50; 95% CI [0.16, 0.84]) and stable 6 months after treatment (d = 0.63; 95% CI [0.24, 1.02]). Treatment adherence was high, 22 out of 29 adolescents completed the treatment.

4.2 STUDY II

There was a significant larger pre- to posttreatment change for the Internet-CBT group compared with the control group on the GSRS-IBS (B = -6.42, p =.006, effect size Cohen's d = 0.45, 95% CI [0.12, 0.77]), and on almost all secondary outcomes,. After 6 months the results were stable or significantly improved.

4.3 STUDY III

We found that change in avoidant behavior, but not perceived stress, mediated the effect of exposure-based ICBT on GI symptoms. The decrease in avoidant behavior explained a large part (67%) of the total treatment effect. The control for a unidirectional relationship over time between avoidant behavior and GI symptoms, showed that a change in avoidant behavior predicted a later change in GI symptoms, but not the other way around.

4.4 STUDY IV

Adherence to treatment was acceptable with an average of 7.2 completed modules out of ten, including the six (19.4%) adolescents that dropped out from treatment. The adolescents reported the treatment to be credible, an overall satisfaction with the treatment, and good

alliance with their therapist. The improvement on the primary outcome, pain intensity, from pretreatment to posttreatment was significant with a large effect size (Cohen's $d = 0.96$, $p <$ .001, 95% CI [0.37, 1.56]). The adolescents also made significant and large improvements on secondary outcomes, such as gastrointestinal symptoms ($d = 0.86$, $p < .001$) and quality of life ($d = 0.91$, $p < .001$).

5 DISCUSSION

The studies included in this thesis show that exposure-based Internet-CBT is feasible and potentially effective to reduce gastrointestinal symptoms, fear of symptoms and pain interference for adolescents with FGID (Study I), also when specifically tailored for FAP and FD (Study IV). The Internet-CBT was found to effectively reduce gastrointestinal symptoms, pain intensity, fear of symptoms, school absenteeism, and improve quality of life for adolescents with IBS, compared to a wait-list (Study II). The exposure-based Internet-CBT reduces avoidant behavior, a process which mediates a reduction in gastrointestinal symptoms (Study III).

5.1 IS INTERNET-CBT FEASIBLE FOR ADOLESCENT FGID?

To answer this question two studies were conducted, Study I that included adolescents with IBS, FAP or FD, and Study IV that included adolescents with FAP or FD only.

The adolescents in Study I showed good adherence to the treatment, with low attrition rates, and significant and moderately-sized improvements from pretreatment to posttreatment in gastrointestinal symptoms, pain reactivity, and pain interference. The improvements were stable after 6 months. Hence, the treatment seemed to be feasible as well as potentially effective for adolescents with FGID.

However, since the overall treatment effect in Study I, even though comparable to other studies on pediatric FGIDs, differed from the strong effects seen in adult studies, there was reason to review the treatment for all diagnoses, before we went on to conduct a randomized trial.

In Study I the exposure exercises were limited to four weeks with two bi-weekly modules. The adolescents may have needed more time for exposure, and more support during the time for the exposure exercises. Furthermore, some adolescents had reported using the mindfulness and acceptance exercises as a means to immediately reduce GI symptoms, which was not the intention as it was contrary to the purpose of exposure, i.e., new learning in the presence of symptoms. Consequently, we decided to prolong the protocol to ten weekly sessions, emphasizing exposure and minimizing any other exercises.

In addition, there were some observed, although not significant, differences between adolescents with IBS compared to adolescents with FAP/FD. Half of the adolescents with

FAP/FD dropped out of treatment (n = 5), and those who completed the treatment did not seem to benefit from the treatment to the same extent as those who had IBS. As only 10 of the included adolescents had FAP/FD, it was difficult to detect any significant differences in subgroup analyses. We suspected however, that the treatment might have been insufficiently adapted for FAP/FD, as it was derived from a treatment for adult IBS. Also, because IBS is the most common diagnosis among adolescents with FGID, most examples in the treatment described IBS-specific behavior. IBS-specific behavior are often the behaviors linked to the disturbed defecation pattern, which may evoke disgust and be something that other adolescents do not want to be associated with. Our clinical impression confirmed that this was the case for some participants with FAP/FD, which may have caused a lower adherence, and thereby a weaker treatment effect. Furthermore, the primary outcome, global gastrointestinal symptoms as measured by the GSRS-IBS, includes a wide range of IBS symptoms. As the adolescents with FAP/FD had a narrow range of gastrointestinal symptoms, there might have been a floor effect on the GSRS-IBS for this subgroup.

Accordingly, a new prolonged treatment protocol was developed for adolescent FAP/FD leaving out all examples that referred only to IBS-symptoms, and including more examples related to FAP/FD symptoms and behavior. Furthermore, the primary outcome, pain intensity, was selected to better fit the group. With all these changes for FAP/FD, there was a need for a new feasibility study, to give the treatment a reasonable chance to show preliminary effects before it is compared in a large randomized trial (68), which led to Study IV.

The adolescents in the Internet-CBT specifically adapted for FAP or FD, Study IV, showed good adherence, and reported high treatment credibility as well as satisfaction with the treatment. There were significant positive changes from pretreatment to posttreatment on the primary outcome, pain intensity, as well as on most secondary outcomes such as quality of life and global gastrointestinal symptoms, with large within-group effect sizes. The parents reported significant improvement with large effect sizes on their child's gastrointestinal symptoms and quality of life, as well as a reduction in parental protectiveness and monitoring of their child's symptoms. The treatment, when prolonged and adapted to FAP/FD seemed to be not only feasible for the group, but also potentially more effective than the prior treatment in Study I.

The adherence in both Study I and Study IV was high compared to adherence reported in recent meta-analysis on adult Internet-CBT (69), and comparable to prior studies on adherence in adult Internet-CBT (70,71). Notably, the adolescents in Study IV rated a good

alliance with their therapist (a variable not assessed in Study I) despite the limited therapist contact, a phenomenon earlier reported in adult Internet-CBT (72) and Internet-CBT for adolescents with OCD (73). There are indications that a perceived alliance with the therapist can increase the motivation to continue treatment (74), but there is also evidence that good perceived alliance in itself does not increase the efficacy of internet-delivered treatments. (75). For the acceptability of the treatment, factors such as credibility, alliance and treatment satisfaction are probably important. In a treatment as demanding as an exposure treatment for pain and other unpleasant abdominal symptoms, the acceptance of the treatment and adherence to the treatment are important indicators that the participants perceive the treatment as feasible.

There are many possible explanations for the large effect sizes in Study IV. The most obvious reason, beside the more extensive adaptation to the specific diagnoses, is the longer treatment duration. The treatment in this study was prolonged in the same manner as the treatment in Study II, which possibly affected the treatment effect. Also, the therapists were more experienced in delivering the treatment at the time for Study IV, and may have been more effective as therapists in Study IV, compared to Study I. Furthermore, several outcome measures were replaced or changed to better correspond with the symptoms that adolescents with FAP/FD report, yielding greater opportunity to capture a change in symptoms.

5.1.1 Concluding remarks regarding feasibility of ICBT for FGID

We cannot know for certain if it is the adaptation of the treatment content to the diagnoses, other above-mentioned changes made, or any possible differences between the samples, that provided larger effect sizes in Study IV, compared to Study I. However, it seems to be more effective to use a longer treatment format with weekly therapist support, and adapt examples and exercises to specific diagnoses. What we can conclude is that exposure-based Internet CBT is feasible for IBS, FAP and FD, and provides potentially positive effects on both the gastrointestinal symptoms, as well as secondary outcome measures, such as fear of symptoms and quality of life. The reported satisfaction with the treatment and good alliance with the therapist shows that the treatment can be delivered over the internet, and that it is acceptable to use exposure for abdominal pain and other GI-symptoms.

5.1 IS INTERNET-CBT EFFECTIVE FOR ADOLESCENT IBS?

To investigate if the treatment could be more effective for adolescents IBS than the natural course of the diagnosis, we conducted Study II, a randomized controlled trial comparing the 10-week long exposure-based Internet-CBT to a wait-list control.

The adolescents in the treatment group in Study II had a significantly stronger improvement than the wait-list on the primary outcome, gastrointestinal symptoms as measured with the GSRS-IBS, as well as on most secondary outcomes, such as pain intensity and frequency, fear and worry about symptoms, school absenteeism and quality of life. The results were confirmed by the parents' reports. At six-month follow-up, the treatment gains were either stable or further improved compared to posttreatment. Exposure-based Internet-CBT seems to be effective for adolescents with IBS compared to a wait-list control, with stable or improving long-term effects.

As in Study I, the effect-sizes were lower than in the adult studies on exposure-based Internet-CBT for IBS (49,50,76). However, the adolescents reported a considerably lower level of gastrointestinal symptoms on the GSRS-IBS at baseline than adults with IBS have reported, with a difference between one half and one standard deviation. A low initial symptom level gives little room for improvement during treatment and hence, lower effect sizes. Despite the limited scope for improvement, the adolescents showed a significant improvement on the GSRS-IBS.

Furthermore, although the treatment group improved more, the wait-list control group showed unexpectedly large improvement from pre- to posttreatment. The within-group improvement on the primary outcome was significant with a small effect size (Cohen's d=0.33). Similar improvements were reported on avoidant behavior and perceived stress. This is in contrast to the study that used a wait-list control to examine the effect of exposure-based Internet-CBT for adults with IBS, where no improvement was seen for the participants on the wait-list (49). Prior research on adults on wait-lists have reported a recovery rate corresponding to Cohen's $d = 0.17$ (77), which is substantially less than in our study. The size of the improvement on the wait-list in Study II is comparable to improvements seen in the active controls in studies on children with FAP (43) and chronic pain (78). This might mirror the natural course of the IBS-symptoms earlier mentioned. Even though most adolescents in our study reported several years of problems, indicating chronicity, some participants had only had their problems for a few months at baseline, increasing the likelihood of spontaneous recovery for that subgroup. The weekly assessments might have contributed to

some of the improvement in the wait-list group. Although it was a highly technical procedure, with online assessments and automated sms-reminders, it still might have served as a reminder of the clinical interview and the upcoming treatment, and thereby a kind of attention control. It is also possible that the questions in the weekly measurements gave some clues about how to act or not act in the presence of symptoms, or that assessment fatigue affected the responses.

The relatively broad criteria for pediatric IBS per Rome III is a challenge when conducting treatment trials in this population. Because it might lead to inclusion of participants with quite low levels of symptoms which makes it difficult to obtain large effect sizes, as participants with diverging levels of symptoms introduce increased variance at baseline, and, at least for some, room for improvement is small. However, since everyone in the age group with IBS were included without restrictions on symptom level or functional disability, one might argue that this adds to the ecological validity.

5.1.1 Concluding remarks regarding ICBT for adolescent IBS

Despite the limited scope for improvement and the fact that the adolescents on the wait-list reported significantly improved gastrointestinal symptoms, the adolescents receiving the Internet-CBT reported a significantly larger improvement with a moderate effect-size on the primary outcome ($d = 0.45$), that was stable after 6 months. The steady improvement in gastrointestinal symptoms, along with the width of the improvements seen across almost all secondary outcome measures in favor of the treatment, indicates that exposure-based Internet-CBT is effective for adolescent IBS.

5.2 DO AVOIDANT BEHAVIOR OR PERCEIVED STRESS MEDIATE CHANGE?

The mediational analysis of two competing putative mediators, avoidant behavior and perceived stress, demonstrated that the exposure-based Internet-CBT leads to a reduction in avoidant behavior that mediates a reduction in gastrointestinal symptoms. Control for uni-directionality showed that the opposite relationship did not apply, i.e., the change in gastrointestinal symptoms did not predict subsequent change in avoidance behavior. Thus,

the results confirm that the behavioral pattern, associated with GI anxiety and increased GI symptoms, is an important target in treatment.

Exposure-based CBT for IBS encourages participants to provoke GI symptoms during exposure exercises. The assumption is that harmless visceral sensations have been conditioned as noxious stimuli, and that these stimuli are treated as a threat in the amygdala and initiates behavioral responses as well as physiological changes in the brain. These responses may result in increased fear of the noxious stimuli (79), in this case the GI symptoms. Through exposure, the patient gets in contact with the conditioned stimuli (CS), that elicit fear and worry (80). Exposure is the clinical application of extinction, a process of deconditioning of a learned conditioned pairing of an earlier neutral stimulus with something unpleasant. In a prior mediational analysis on adult IBS, a reduction in fear for symptoms predicted reduction in gastrointestinal symptoms due to exposure-based treatment, which indicates that the extinction process is targeted by the treatment (81).

Robust findings from experimental research have led to the proposition that extinction is not a question of destruction of what has been learned, an unlearning, but rather that extinction gives the opportunity to new learning experiences in the presence of the CS (82). Thus, even if the CS after treatment is associated with more responses that inhibit the conditioned response (CR), the association with the original CR is still there (82). This leaves room for a relapse after exposure treatment, and in rodents a renewal of the CR has been observed after extinction, if the context changes (82). It has therefore been suggested that the CR is independent of context and therefore more readily available for retrieval than the extinction memory when context changes (82). Relapse of CR in another context has also been observed in humans after successful in vivo exposure (83). Repeated exposure in many different contexts has been suggested to prevent relapse (83). Through the analysis of repeated assessment of avoidant behavior, Study III demonstrated that a reduction during treatment in a broad range of IBS-specific behaviors, predicted a reduction in GI symptoms. A reduction in avoidance behavior indicates that the participants do the exposure exercises in many different contexts, and suggest an overall reduction of avoidance in everyday life, not only during planned exposure exercises. The further significant improvement in the treatment group on the IBS-BRQ six months after treatment completion, together with stable treatment gains on gastrointestinal symptoms (84), support the proposition that an overall reduction in avoidant behavior could prevent relapse after treatment conclusion. Through repeated exposure in changing contexts, the original association that visceral sensations from the

abdomen is a threat may have weakened, as many inhibiting associations have possibly been formed over time (85).

Perceived stress decreased equally in both groups, and could therefore not function as a mediator of the difference between the groups in symptom level improvement. Importantly, the treatment group decreased significantly more in the primary outcome, GI symptoms, and this was found to be mediated by avoidance behavior and not a reduction in perceived stress. Thus, although the mediation analysis cannot rule out that reduced stress can potentially lead to reduced symptom, it can be concluded that it is not necessary to target stress in treatment for symptom improvement.

5.2.1 Concluding remarks regarding mediators of change

Study III demonstrated that a prior reduction in avoidant behavior predicts a reduction in gastrointestinal symptoms, due to treatment. A reduction in perceived stress is not related to the treatment, and did therefore not predict a later change in gastrointestinal symptoms, due to the treatment. Despite the common use of stress reducing components in other CBT-treatments for pediatric FGID, such as relaxation or identification of stressors, this seems to be the first study within the field that has investigated a reduction in stress as a potential mediator. In this study we had weekly assessments of mediators and outcome during treatment, which gave the opportunity to do proper time-lagged analyses, that control for the occurrence of a change in the mediator before a change in the outcome. To the best of my knowledge, this has not been done before in the field of pediatric FGID, nor pediatric chronic pain. Weekly assessments require that the potential mediators are defined in advance, which increases the possibility that the potential mediators are theoretically based, and prevents exploratory post-hoc analyzes that could allow for random findings.

5.3 LIMITATIONS

There are some limitations that must be considered when interpreting the results from the studies included in the thesis. Study I and Study IV had an obvious limitation in the uncontrolled design to be able to draw conclusions on efficacy. An uncontrolled design cannot control for the natural course of FGID over time. Notably, most adolescents in Study

IV reported chronic symptoms, which made a spontaneous reduction during treatment less likely. The design is also somewhat of a limitation in Study II, because a wait-list could not control for attention, expectation of treatment and other unspecific effects from an active treatment. However, the unexpected improvement in the wait-list indicates that the wait-list somehow was affected, either by natural recovery, or that the weekly assessments acted as attention control. The mediators in Study III were chosen to investigate two competing theories on mechanisms of change in IBS-treatment, stress or the behavioral pattern related to GI anxiety. However, the outcome measures to assess the mediators tapped into different dimensions. The PSS does not measure stress behavior, but the perception of feelings of stress, while the IBS-BRQ do measure self-reported behavior, and not perception of feelings related to avoidance. There is a risk that these two dimensions are not entirely comparable. Notably, the PSS has been shown to predict health-related behavior, such as use of health care (64), and may be an adequate proxy to stress-related behavior. Also, the Internet-CBT investigated in these trials does not target a reduction in stress, but rather encourages an increase in stress, if participants use avoidance of stress as a strategy to control symptoms. If stress reduction had been an important part of the treatment, it is possible that a reduction in stress could prove to mediate a reduction in gastrointestinal symptoms. Furthermore, the adolescents included in the trials might not be totally representative of the adolescent population with FGIDs, as the thorough inclusion procedure probably demanded quite a high motivation to receive help, as well as supportive parents.

5.4   IMPLICATIONS FOR FUTURE RESEARCH

The findings in this thesis have some implications for future research. There is a need for replications with active control conditions. Although a waitlist is a valid control for pediatric FGID, as there is currently no standard medical treatment, a waitlist cannot control for the placebo-effect that is well-known to be quite effective in the population (86). A credible active control ensures that an effect from the exposure-based treatment is not solely the result of the participants' expectations to improve from treatment, or attention and general support from a therapist. Although there are some indications that the treatment in our study may be more effective than treatments in previous large studies (43,44,78), given the width of positive change across multiple dimensions and the stable and even increasing improvements six months after treatment, we cannot be sure that exposure-based Internet-CBT is more

effective than other psychological treatments for adolescent IBS, before this has been demonstrated in studies with active controls. Evidently, a randomized controlled trial is also needed to investigate the efficacy of the treatment for adolescent FAP/FD, as this has not been done.

There is also a need for further investigation into the mechanisms of change. The mediation study implicates that avoidant behavior is an important treatment target, and might also indicate that the mechanism of extinction of GI-anxiety is targeted in the treatment. However, this needs to be consistently demonstrated in replication studies (87). Avoidant behavior as a mediator would also need to be compared to other competing or complementing mediators, such as fear of symptoms, to better understand the mechanism of change in an exposure-based treatment. If a reduction in avoidant behavior could predict a reduction in fear of symptoms, it would be further proof that the treatment acts through the extinction process, that is, exposure leads to opportunities for new learning, which in turn reduces fear of symptoms. If, on the other hand, fear predicts change in avoidant behavior, it could suggest that there rather is a cognitive process activated that reduces catastrophizing, and thereby reduces the anticipation anxiety. This would be important information to better optimize the treatment. In the treatment of pediatric FGID, it is also important to investigate the role of the parents, such as if a change in the parents' protective behavior could predict a later change in their adolescent's gastrointestinal symptoms, or if it is a prior reduction in the adolescent's symptomatic level that predicts a reduction in parental protective behavior. Furthermore, stress reduction may be more important than the mediational analysis demonstrated, when also targeted in treatment.

As one argument for internet-delivered treatments is the cost-effectiveness, which has been observed in adults (88), there is a need for studies investigating the cost-effectiveness for pediatric Internet-CBT. There are important differences in the treatment of children and adolescents compared to adults, such as more therapist-time per family and more detailed inclusion procedures to minimize risk, which may have impact on the treatment's cost-effectiveness.

The scarce availability to effective treatments for pediatric FGIDs, makes it relevant to quickly disseminate a treatment that has proven efficacy in regular healthcare. That would require studies examining how such dissemination can be done while maintaining efficacy, and what processes are required for the treatment to be accepted as a viable treatment option in regular care.

6 CONCLUSION

Exposure-based Internet-CBT is a feasible treatment for adolescent FGID. The treatment can effectively improve gastrointestinal symptoms, pain intensity and frequency, quality of life, avoidant behavior and fear and worry about symptoms in adolescent IBS, with stable or increasing long-term effects. It is also a feasible and potential effective treatment for FAP and FD, when specifically tailored for the diagnoses. Exposure-based Internet-CBT gives a reduction in avoidant behavior that mediates a subsequent change in gastrointestinal symptoms. Stress reduction does not seem to be a necessary target in treatment to improve GI-symptoms. The work in this thesis can contribute to increased access to effective treatment for the many adolescents who suffer from FGID.

7 ACKNOWLEDGEMENTS

The studies included in this thesis are far from a one-woman show. From the very first moment, there have been many people involved. I have at least as many reasons to be grateful to you all, of which I will mention only a few here.

Brjánn Ljótsson when you invited me into this research project in the autumn 2011, I had no idea what I accepted to do, and I knew that. What I didn´t know was how much hard work that can be fitted in to a week, a month, a year or several. You taught me that, mainly through modeling. I used to think R was a letter, or maybe the symbol for resistance, now I know it´s a beautiful language to communicate data analysis with a computer, as long as you know how to talk the talk (I intend to keep you as my interpreter). I had never thought about how many tiny details that are tightly squeezed into an article, and how important it is to make it exactly right because "there will always be at least one reviewer who have Asperger". Furthermore, I had never used much of the words Furthermore, Hence or "Anywho", but have come to understand how convenient they are. Brjánn, in addition to being the best main supervisor who has that rare deep knowledge of statistics and behavioral research, you have over the years given me so generously of your time, created a beautiful research group with a warm and comfortable atmosphere, been an entertaining companion to conferences in Chicago, San Diego and London, and have become a dear friend of mine.

Ola Olén, thank you for seeing the opportunity, and taking the initiative for these studies. For grant writing at a speed that must be at the elite level, which gave results. For all lectures, and all contacts with physicians throughout Sweden, to inform about the study. For your deep voice and trustworthy appearance, that is so perfect on TV. For your patience with me when I wanted your attention, and never learned your clinic schedule. For your advice and wise comments during the writing of applications and articles. For humming us all through the streets of Chicago, and for climbing that horse (I am looking forward to ESPGHAN in Prague this spring). But most of all, for your faith in my abilities, and your unwavering support. With your guidance, I am looking forward to learn more about epidemiological studies.

Eva Serlachius, you gave our studies a home when they were barely an embryo, and the ChildInternetProject (BiP) still a fragile baby. Thank you for being so brave! You brought our studies a stability and a framework, firm and gently. I'm very grateful that you introduced me to new research collaborations during my last year as PhD-student. It is invaluable. I do admire what you have accomplished with resolute endurance, brilliant understanding of how

to anchor a research unit within an organization, and a good sense of high quality research. I am proud to have got to be a small part of the ever growing BiP, which you have built up.

Erik Hedman, my fourth supervisor (I needed many, apparently). You brought brilliance, speed and energy into the project, for which I am very grateful. If I ever want to do a really advanced study with incredibly intricate design, I know where to turn. Manuscript-writing would not have been half as much fun, without your comments (and the papers not as well-written).

Maria Lalouni, what would I have done without you? When you began your PhD-project, you immediately showed your determined dedication and critically reviewed everything we had done (including <u>each</u> item in our 260-items questionnaire), I had some tough eye-openers, and learned many really good things from you. You've been the most loyal, smart, considerate and funny colleague I could have wished for. Together, we have really accomplished something here. Most of all, you are a very dear friend. And when you tell me that you wake up in the middle of the night, out of fear that you have forgotten my birthday, I feel that we have a deep connection. You didn´t forget. This year.

The Brjánn Ljótsson research group: Hanna Sahlin, Johan Bjureberg, Josefin Särnholm (and Maria and Brjánn, of course). In this group of extraordinary nice, brilliant and lovely people, no questions are too stupid, which is lucky for me. Nerding into statistical details have been a pure pleasure with you, and I think my brain might have expanded a little (that might be an ordinary headache). Hope to see you all in Westeros, soon again.

I also would like to thank, in random order:

All adolescents and parents that participated in our studies, for enduring all our questions and doing your best in our treatment. **All physicians** around Sweden that referred participants to our studies, we couldn't have done without you. **Johanna Engelbrektsson (Andersson),** the incredible number of potential and actual participants that you handled so beautifully, thank you for everything! **Mari Ljungström** and **Tove Sundqvist**, for administrative help (that is, hundreds of phone-calls and hours on our platforms to register people). **Gabriella Carpelan** for collecting follow-up assessments more thoroughly than any of us could have done (Can we keep you forever, Gabriella?). **Bo Melin** and **Lotta Spangenberg** for believing in our studies from the very beginning, and **Peter Ericsson** and **Joanna Crafoord** for continuing that support. **Marc Benninga** and **Magnus Simrén** for helpful experienced advice. **Matteo Bottai** for exquisite lectures on Biostatistics during the Research School, and crucial help with the statistics in the RCT. **Fredrik Santoft**, for being a reliant and super-fast

8 REFERENCES

1.   Spee LAA, Lisman-van Leeuwen Y, Benninga MA, Bierma-Zeinstra SMA, Berger MY. Prevalence, characteristics, and management of childhood functional abdominal pain in general practice. Scand J Prim Health Care. 2013 Dec;31(4):197–202.

2.   Varni JW, Bendo CB, Nurko S, Shulman RJ, Self MM, Franciosi JP, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. J Pediatr. 2015 Jan;166(1):85–90.

3.   Saps M, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C. A prospective school-based study of abdominal pain and other common somatic complaints in children. J Pediatr. 2009 Mar;154(3):322–6.

4.   Dhroove G, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? J Pediatr Gastroenterol Nutr. 2010 Nov;51(5):579–83.

5.   Patterns and predictors of health service utilization in adolescents with pain: comparison between a community and a clinical pain sample. J Pain. 2011 Jul;12(7):747–55.

6.   Park R, Mikami S, LeClair J, Bollom A, Lembo C, Sethi S, et al. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. Neurogastroenterol Motil. 2015 May;27(5):684–92.

7.   Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology. 2016 Feb 19;150(6):1262–2.

8.   Rasquin A. History and Definition of the Rome Criteria. In: Pediatric Neurogastroenterology. Totowa, NJ: Humana Press; 2012. pp. 325–9.

9.   Apley J, Naish N. Recurrent Abdominal Pains: A Field Survey of 1,000 School Children. Arch Dis Child. BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health; 1958 Apr 1;33(168):165–70.

10.   Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al. Childhood functional gastrointestinal disorders. Gut. 1999 Sep 1;45(Supplement 2):ii60–8.

11.   Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006 Apr;130(5):1527–37.

12.   Hyams JS, Di Lorenzo C, Saps M, Schulman R, Staiano A, Van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology. 2016 Feb 15;150(6):1456–1468.e2.

13.   Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. Zhang L, editor. PLoS ONE. 2015;10(5):e0126982.

14.   Lewis ML, Palsson OS, Whitehead WE, van Tilburg MAL. Prevalence of Functional

Gastrointestinal Disorders in Children and Adolescents. J Pediatr. 2016 Oct 1;177:39–43.e3.

15. Olén O, Neuman Å, Koopmann B, Ludvigsson JF, Ballardini N, Westman M, et al. Allergy-related diseases and recurrent abdominal pain during childhood - a birth cohort study. Aliment Pharmacol Ther. 2014 Dec;40(11-12):1349–58.

16. Chitkara DK, van Tilburg MAL, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol. 2008 Mar;103(3):765–74–quiz775.

17. Horst S, Shelby G, Anderson J, Acra S, Polk DB, Saville BR, et al. Predicting persistence of functional abdominal pain from childhood into young adulthood. Clin Gastroenterol Hepatol. 2014 Dec;12(12):2026–32.

18. Shelby GD, Shirkey KC, Sherman AL, Beck JE, Haman K, Shears AR, et al. Functional abdominal pain in childhood and long-term vulnerability to anxiety disorders. Pediatrics. 2013 Sep;132(3):475–82.

19. Cunningham NR, Cohen MB, Farrell MK, Mezoff AG, Lynch-Jordan A, Kashikar-Zuck S. Concordant parent-child reports of anxiety predict impairment in youth with functional abdominal pain. J Pediatr Gastroenterol Nutr. 2015 Mar;60(3):312–7.

20. Van Oudenhove L, Crowell MD, Drossman DA, Halpert AD, Keefer L, Lackner JM, et al. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. Gastroenterology. 2016 Feb;150(6):1355-1367.

21. Mayer EA, Naliboff BD, Chang L. Stress and the gastrointestinal tract V. stress and irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2001 April;280(4):519-524.

22. Mayer EA, Tillisch K. The Brain-Gut Axis in Abdominal Pain Syndromes. Annual Review of Medicine. 2011;62(1):381–96.

23. Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Cochrane Database Syst Rev. 2008;(1):CD003017.

24. Korterink JJ, Rutten JMTM, Venmans L, Benninga MA, Tabbers MM. Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. J Pediatr. 2015 Feb;166(2):424–6.

25. Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane database of systematic reviews (Online). 2011;(7):CD008013.

26. Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C. Dietary interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Huertas-Ceballos AA, editor. Cochrane database of systematic reviews (Online).; 2009;(1):CD003019.

27. Rutten JMTM, Korterink JJ, Venmans LMAJ, Benninga MA, Tabbers MM. Nonpharmacologic Treatment of Functional Abdominal Pain Disorders: A

Systematic Review. Pediatrics. 2015 Feb 9;135(3):522–35.

28. Giannetti E, Staiano A. Probiotics for Irritable Bowel Syndrome: Clinical Data in Children. J Pediatr Gastroenterol Nutr. 2016;63(Suppl1)S25–6.

29. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis. Clin Psychol Rev. 2016 Nov 8;51:142–52.

30. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2015 Mar;12(3):159–71.

31. Vlieger AM, Menko Frankenhuis C, Wolfkamp SCS, Tromp E, Benninga MA. Hypnotherapy for Children With Functional Abdominal Pain or Irritable Bowel Syndrome: A Randomized Controlled Trial. Gastroenterology. Elsevier; 2007 Jan 11;133(5):1430–6.

32. Vlieger AM, Rutten JMTM, Govers AMAP, Frankenhuis C, Benninga MA. Long-Term Follow-Up of Gut-Directed Hypnotherapy vs. Standard Care in Children With Functional Abdominal Pain or Irritable Bowel Syndrome. Am J Gastroenterol. 2012 Feb 7;107(4):627–31.

33. van Tilburg MAL, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M, et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. Pediatrics. 2009;124(5):e890–7.

34. Gulewitsch MD, Müller J, Hautzinger M, Schlarb AA. Brief hypnotherapeutic-behavioral intervention for functional abdominal pain and irritable bowel syndrome in childhood: a randomized controlled trial. Eur J Pediatr. 2013 Aug;172(8):1043–51.

35. Wallander JL, Madan-Swain A, Klapow J, Saeed S. A randomised controlled trial of written self-disclosure for functional recurrent abdominal pain in youth. Psychology and Health. Taylor & Francis; 2011;26(4):433–47.

36. Alfvén G, Lindstrom A. A new method for the treatment of recurrent abdominal pain of prolonged negative stress origin. Acta paediatrica. 2007 Jan;96(1):76–81.

37. Eccleston, Palermo TM, Williams AC de C, Lewandowski Holley A, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane database of systematic reviews (Online). 2014;5:CD003968.

38. Sanders MR, Rebgetz M, Morrison M, Bor W, et al. Cognitive-behavioral treatment of recurrent nonspecific abdominal pain in children: An analysis of generalization, maintenance, and side effects. J Consult Clin Psychol. 1989;57(2):294–300.

39. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: A controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol. 1994;62(2):306–14.

40. Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a

cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol. 2002;30(5):397–408.

41. Hicks CL, Baeyer von CL, McGrath PJ. Online psychological treatment for pediatric recurrent pain: a randomized evaluation. J Pediatr Psychol. Oxford University Press; 2006 Aug;31(7):724–36.

42. Duarte M, Penna F, Andrade E, Cancela C, Neto J, Barbosa T. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr. 2006;43(1):59–64.

43. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. Am J Gastroenterol. 2010 Mar 9;105(4):946–56.

44. Van Der Veek SMC, Derkx BHF, Benninga MA, Boer F, De Haan E. Cognitive behavior therapy for pediatric functional abdominal pain: a randomized controlled trial. Pediatrics. 2013 Nov;132(5):e1163–72.

45. Palermo TM, Wilson AC, Peters M, Lewandowski A, Somhegyi H. Randomized controlled trial of an Internet-delivered family cognitive-behavioral therapy intervention for children and adolescents with chronic pain. Pain. 2009 Nov;146(1-2):205–13.

46. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain. 2016 Jan;157(1):174–85.

47. Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology. 2006 Apr;130(5):1447–58.

48. Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C. Psychosocial interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Huertas-Ceballos AA, editor. Cochrane database of systematic reviews. 2008;(1):CD003014.

49. Ljótsson B, Falk L, Vesterlund AW, Hedman E, Lindfors P, Ruck C, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome--a randomized controlled trial. Behav Res Ther. 2010 Jun;48(6):531–9.

50. Ljótsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, et al. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. Nature Publishing Group; 2011 Aug;106(8):1481–91.

51. Ljótsson B, Hesser H, Andersson E, Lackner JM, Alaoui El S, Falk L, et al. Provoking symptoms to relieve symptoms: a randomized controlled dismantling study of exposure therapy in irritable bowel syndrome. Behav Res Ther. 2014 Apr;55:27–39.

52. Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry. 2001;62 Suppl 8:28–36–discussion37.

53. Labus JS, Mayer EA, Chang L, Bolus R, Naliboff BD. The central role of gastrointestinal-specific anxiety in irritable bowel syndrome: further validation of the visceral sensitivity index. Psychosom Med. 2007 Jan;69(1):89–98.

54. Reme SE, Darnley S, Kennedy T, Chalder T. The development of the irritable bowel syndrome-behavioral responses questionnaire. J Psychosom Res. 2010 Sep;69(3):319–25.

55. Mowrer O. On the dual nature of learning—a re-interpretation of conditioning and problem-solving. Harvard Educational Review. 1947; 17:102-148.

56. Bolles RC, Stokes LW, Younger MS. Does CS termination reinforce avoidance behavior? J Comp Physiol Psychol. 1966;62(2):201–7.

57. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000 Apr;85(3):317–32.

58. Vigerland S, Lenhard F, Bonnert M, Lalouni M, Hedman E, Ahlen J, et al. Internet-delivered cognitive behavior therapy for children and adolescents: A systematic review and meta-analysis. Clin Psychol Rev. 2016;50:1–10.

59. Waller G. Evidence-based treatment and therapist drift. Behav Res Ther. 2009 Feb;47(2):119–27.

60. Hedman E, Ljótsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. Expert Rev Pharmacoecon Outcomes Res. 2012;12(6):745–64.

61. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Assessment. 2015;45(16):3357-3376.

62. Wiklund IK, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, et al. An irritable bowel syndrome-specific symptom questionnaire: development and validation. Scand J Gastroenterol. 2003 Sep;38(9):947–54.

63. Cohen J. A power primer. Psychol Bull. 1992;112(1):155–9.

64. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983 Dec;24(4):385–96.

65. MacKinnon DP, MacKinnon DP, Fairchild AJ, Fairchild AJ, Fritz MS, Fritz MS. Mediation analysis. Annu Rev Psychol. 2007; 58: 593-614.

66. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879–91.

67. Hicks CL, Baeyer von CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain. 2001 Aug;93(2):173–83.

68. Mohr DC, Spring B, Freedland KE, Beckner V, Arean P, Hollon SD, et al. The selection and design of control conditions for randomized controlled trials of

psychological interventions. Psychother Psychosom. 2009;78(5):275–84.

69. Wildeboer G, Kelders SM, van Gemert-Pijnen JEWC. The relationship between persuasive technology principles, adherence and effect of web-Based interventions for mental health: A meta-analysis. Int J Med Inform. 2016 Apr; 96: 71-85.

70. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev. 2012 Jun;32(4):329–42.

71. van Ballegooijen W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, et al. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. PLoS ONE. 2014;9(7):e100674.

72. Andersson G, Paxling B, Wiwe M, Vernmark K, Felix CB, Lundborg L, et al. Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. Behav Res Ther. 2012;50(9):544–50.

73. Lenhard F, Vigerland S, Engberg H, Hallberg A, Thermaenius H, Serlachius E. "On My Own, but Not Alone" - Adolescents' Experiences of Internet-Delivered Cognitive Behavior Therapy for Obsessive-Compulsive Disorder. PLoS ONE. 2016;11(10):e0164311.

74. Donkin L, Glozier N. Motivators and motivations to persist with online psychological interventions: a qualitative study of treatment completers. J Med Internet Res. 2012 Jun 22;14(3):e91.

75. Andersson G, Paxling B, Wiwe M, Vernmark K, Felix CB, Lundborg L, et al. Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. Behav Res Ther. 2012 Sep;50(9):544–50.

76. Ljótsson B, Andersson G, Andersson E, Hedman E, Lindfors P, Andréewitch S, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology. 2011 Oct; 11(1):110.

77. Hesser H, Weise C, Rief W, Andersson G. The effect of waiting: A meta-analysis of wait-list control groups in trials for tinnitus distress. J Psychosom Res. 2011 Apr; 70(4):378-384.

78. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain. 2016 Jan;157(1):174–85.

79. LeDoux JE, Pine DS. Using Neuroscience to Help Understand Fear and Anxiety: A Two-System Framework. Am J Psychiatry. 2016 Nov 1;173(11):1083–93.

80. LeDoux J. Anxious. Vol. 53, Journal of Behavior Therapy and Experimental Psychiatry. Penguin; 2016.

81. Ljótsson B, Hesser H, Andersson E, Lindfors P, Hursti T, Ruck C, et al. Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. J Consult Clin Psychol. 2013 Dec;81(6):1113–26.

82. Bouton ME. Context and Behavioral Processes in Extinction. Learn Mem. 2004;11(5):485–94.

83. Vervliet B, Vervliet B, Craske MG, Craske MG, Hermans D, Hermans D. Fear extinction and relapse: state of the art. Annu Rev Clin Psychol. 2013;9:215–48.

84. Bonnert M, Olén O, Lalouni M, Benninga MA, Bottai M, Engelbrektsson J, et al. Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial. Am J Gastroenterol. 2016 Nov (Advance online publication).

85. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: An inhibitory learning approach. Behav Res Ther. 2014;58:10–23.

86. Benninga MA, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. Gastroenterology. 2009 Oct;137(4):1207–10.

87. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007;3:1–27.

88. Donker T, Blankers M, Hedman E, Ljotsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med. 2015 Aug 3;45(16):3357–76.