General introduction
Definition of Functional Constipation (FC)

The diagnosis functional constipation (FC) is based on a complex of symptoms in the absence of an organic cause. For many years, no universal accepted definition was available hampering clinicians to make a diagnosis and researchers to study the same functional disorder. To reach consensus about the definition of FC criteria were formulated and redefined which finally lead to the formulation of the Rome III criteria in 2006 (1;2). Table 1 shows the Rome III criteria. The main characteristics of constipation are infrequent, hard and painful defecation accompanied by the involuntary loss of feces in the underwear. In addition, children with FC may suffer of abdominal pain, abdominal distension, anorexia, vomiting, diminished appetite and urinary incontinence as well. Furthermore, these children often experience straining during defecation. In a minority of cases one finds anal fissures or hemorrhoids (3).

The Rome-III criteria abandoned the terms soiling (4) and encopresis (5;6), used for decades, and adopted the more neutral term fecal incontinence. Based on medical history, physical examination and if necessary diagnostic testing organic fecal incontinence can be distinguished from functional fecal incontinence. The latter is subdivided into constipation-associated fecal incontinence and functional non-retentive fecal incontinence (FNRFI). FNRFI is a separate defecation disorder defined as fecal incontinence in the absence of clinical and physical signs of constipation. As this thesis focuses on FC, FNRFI will not be discussed.

Table 1. Rome III criteria for pediatric functional constipation

<table>
<thead>
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<th>Must include two or more of the following*:</th>
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<tr>
<td>Two or fewer defecations in the toilet per week</td>
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<tr>
<td>At least one episode of fecal incontinence per week</td>
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<td>History of retentive posturing or excessive volitional stool retention</td>
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<tr>
<td>History of painful or hard bowel movements</td>
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<tr>
<td>Presence of a large fecal mass in the rectum</td>
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<td>History of large-diameter stool which may obstruct the toilet</td>
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*Symptoms need to be present at least one month in infants up to 4 years of age, while for children of 4 years or older a minimum period of two months is stated.

Prevalence and cost implications

FC in childhood is a worldwide problem with a prevalence ranging between 0.7%-29.6% with similar prevalence rates for boys and girls (7). The large range is likely due to variations in sample size, different methods of data collections and the lack of consensus about the definition of FC. The prevalence rates for FC of 22.6% in primary care clinics in the United States (8) and 45% in our gastrointestinal outpatient clinic in a tertiary hospital (3) show the great impact of this chronic defecation disorder on health care. A recent study on health care costs of children with constipation in the United States showed that the costs per year are three times higher compared with children without constipation and is roughly of the same magnitude as those for asthma and attention deficit-hyperactivity disorder (9).
Development and maintenance of constipation: the biopsychosocial model

To (theoretically) better understand the development and maintenance of FC as well as to guide treatment, the biopsychosocial model should be considered (10-14). This model is a general model that posits that illness is the result from the interplay between biological, psychological (thoughts, emotions and behavior), and social factors (15).

Stool-withholding behavior as a result of fear for painful defecation is viewed as the major factor in the development and maintenance of FC in children (1;11;13;14;16-21). There are three vulnerable periods that have the potential to change defecation into an unpleasant experience (20;22): 1) dietary transition in infants (<1 years); the change from breast milk to cow’s milk or from formulas to solid food may alter stool characteristics 2) toilet training in toddlers (aged 1-3 years); the time of toilet training is a critical period of emotional struggle between a child who is trying to establish independence and parents who are trying to eliminate diapers 3) the start of school (age of 4 years); children have to utilize unfamiliar toilets. When previous bowel movements were painful and frightening this aversive learning experience can encourage the child to ignore rectal distension cues (urge to defecate) and/or to avoid (going to the toilet) to have a bowel movement. The association of bowel movements with pain becomes conditioned. The urge for defecation becomes a trigger for the child to consciously or unconsciously contract the external anal sphincter and the gluteal muscles. In this way the child controls the bowel movement and avoids pain. This stool withholding behavior becomes a habitual response. The retained stools become harder and larger and more painful to evacuate leading to even more fear and avoidance of defecation. This abnormal defecation pattern then contributes to the development of, or maintenance of, constipation. Moreover, retained stools cause chronic distension of the rectum which will subsequently lead to overflow incontinence, a terrible symptom for both parent and child (19). Together with toileting resistance, continued fecal incontinence can be a source of conflict between parents and children which then also becomes a contributor to the constipation (13;23). The child and its parents are trapped in a vicious circle. It is also thought that long-term fecal impaction results in impaired rectal function which will contribute to persistence of infrequent defecation (24). Although, multiple physiological aspects have been researched adequate insights in the pathophysiology underlying FC is still lacking (25-28).

Treatment approaches in the 20th and 21st century

The importance of psychological factors in understanding and treating FC and fecal incontinence has long been recognized. The extent to which and how psychological factors were assumed to affect FC depended on theoretical viewpoints that varied during the 20th century and were not typically substantiated by data (23,29).

In the early 20th century a relation was established between fecal incontinence and constipation and several authors proposed fecal incontinence to be a primary medical problem for which the only appropriate treatment was rectal laxatives. From the 1950s fecal incontinence was viewed as a psychosomatic disorder and was, due to the large influence of psychoanalytic theory, assumed to be a direct result of emotional disturbances. In this (traditional) psychosomatic model unresolved and unconsciousness emotional conflicts and
mother-child interaction problems were thought to cause selected physical disorders, such as asthma or fecal incontinence. For almost two decades children with fecal incontinence were treated with psychodynamic psychotherapy in psychiatric settings. It was after a publication of Neale in 1963 (30) about behavioral treatment of fecal incontinence that in the 1960s/1970s a series of publications appeared about this treatment approach based on learning theory. In contrast to the biomedical and psychoanalytic treatment, behavioral therapy tends to concentrate on behavior in the "here and now" than on presumed underlying (pathologic) causes.

It was in the 1970s that the somatic and psychological approaches merged, thereby acknowledging that FC is determined by complicated interactions between biological, psychological and social factors (10). This resulted in combined approaches carried out by pediatricians to treat chronic constipation. Pediatricians argued that automatic referrals for psychiatric treatment without any medical interventions could no longer be justified and they combined laxative treatment with education and behavioral recommendations aimed at promoting regular toileting (31;32). On the other hand, it was also thought that collaboration between mental health and pediatricians is useful for constipated children with additionally behavioral, developmental or academic problems (31;33).

Nowadays clinical practice guidelines for the management of FC are developed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) (16) that prescribe education of the child and parents, behavioral recommendations to restore bowel habits and laxative therapy. Recently the NICE guideline in Great Britain and the Dutch guideline were developed to better recognize, diagnose and treat children with constipation (34;35).

**Behavioral therapy**

Behavioral therapy assumes that adaptive and maladaptive behaviors, although they differ in terms of its impact on the environment, are fundamentally identical because they both follow from the same general principles of learning: classic conditioning and operant conditioning. Classic conditioning is a form of associative learning discovered by Pavlov (1849-1936) (36;37). An initially neutral stimulus becomes a meaningful stimulus (conditioned stimulus=CS), because it is repeatedly linked in space and time with the unconditioned stimulus (UCS) that elicits an innate unconditioned response (UCR). This means that eventually the CS will trigger the conditioned response (CR); a relation is learned between the CS and the US. Operant or instrumental conditioning is a method of learning, discovered by Thorndike (1874-1949) and Skinner (1904-1990), in which behavior occurs because it is followed by a reward (positive reinforcement), punishment or avoidance of punishment (negative reinforcement). The reinforcers or (consequences=C) modify the occurrence and form of the behavior or response (R); a relations is learned between a response and its consequences (36;37). Behavioral therapy makes use of the Stimulus-Organism-Response-Consequences model (SORC) (36;37). In this model, an individual’s behavior (Response) is thought to be a joint function of an eliciting situation (Stimulus), of physiological characteristics and past learning history that the individual brings to the situation (Organism variables), and of immediate environmental variables that maintain the behavior (Consequences). This working model of the problem behavior suggests targets for clinical intervention. In order to eliminate constipation behavioral therapists apply the
techniques of systematic desensitization to reduce or eliminate phobic behavior, reinforcement to encourage adequate toileting behavior and behavioral parent training.

**Systematic desensitization**

The concept of desensitization to phobic situations was first described by Wolpe and is a form of exposure (38). Its basic idea is to connect stimuli that evoke fear to a new response that is incompatible with fear and that will therefore displace the fearful response. The technique characteristically uses muscular relaxation as competing response (38). However, other incompatible elements can also be used such as humor, constructive activities or verbalizations (36;37). Exposure takes place while the patient is in a state of relaxation. Then the patient is exposed to feared stimuli in a hierarchical fashion in which progressively ‘stronger’ anxiety provoking stimuli are presented until the stimuli completely lose their ability to evoke anxiety. The relaxation will compete with and inhibit the anxiety and finally comes to replace the anxiety (36;37).

**Reinforcement**

Reinforcement or reward is an event, behavior, privilege, or material object that will increase the probability of occurrence of any behavior upon which it is contingent (36;37). To stimulate a positive parent-child interaction, it is surely preferable to eliminate a maladaptive behavior by increasing the frequency of a desirable, competing behavior (i.e. having a bowel movement) instead of punishing the child for a maladaptive behavior (i.e. fecal incontinence). To increase the frequency of the desired behavior it is crucial that reinforcers are dispensed contingently; only following desired behavior and dispensed immediately. Extinction is a procedure contrary to reinforcement. It is the nonreinforcement of a maladaptive behavior. This involves ignoring a behavior that previously received reinforcing attention.

**Behavioral parent training**

Among the behavioral therapies, behavioral parent training (BPT) is a well-established treatment for child behavioral, emotional, and developmental problems and is viewed as one of the most effective ways to change parenting (39-44). BPT uses parents as behavior change agents by teaching them the theoretical framework of the operant learning principles with an emphasis on the role parents may play in the development and maintenance of child behavior problems. Moreover, BPT addresses maladaptive parenting by training parents to use effective behavioral management strategies at home. Psycho education and cognitive restructuring of parental cognitions are also important elements of BPT. Parents are taught to identify and manipulate the antecedents and consequences of child behavior, target and monitor problematic behaviors, reward wanted behavior through praise, positive attention, and tangible rewards (implementing token systems), and decrease unwanted behavior through planned ignoring, time out, and other nonphysical discipline techniques. Benefits of behavioral parent training include enhanced knowledge and understanding of the problem behavior in their child, identifying and managing child behavior problems, as well as improving parent-child communication.
Aim, design and outline of the thesis

Behavioral Therapy for Childhood Constipation

The primary aim of this study was to compare the efficacy of behavioral therapy with laxatives to conventional treatment in treating FC in childhood which resulted in the following research question:

1. Is behavioral therapy with laxatives compared with conventional treatment more successful in treating FC, stool-withholding behavior, and emotional and behavior problems?

Theoretical background

Stool-withholding behavior is assumed to play a key role in the development and maintenance of FC in children (1;11;13;14;16-21). In addition, emotional and behavior problems are common in children with FC and fecal incontinence (32;45-48). Because successful treatment for FC and fecal incontinence led to behavioral improvement, it is argued that emotional and behavior problems are secondary and are a consequence of the social impact of fecal incontinence and pain (32;33;49;50). Moreover, it is suggested that treatment of FC in children with behavior problems is less likely to be successful (31-33;50-52). In treating childhood constipation, it seems important to address defecation avoidance and to treat behavior problems. A previous study showed that successful outcome in constipated children was higher in those treated with a structured toileting program with additional laxative therapy compared with those receiving only the structured toileting program (32). Two reviews showed that there is some evidence that behavioral interventions added to laxative therapy has advantage over laxative therapy alone for improving continence in children with constipation-associated fecal incontinence (11;14). Although, many studies report on medical treatment and behavioral interventions, comparison of findings is hampered because descriptions of the interventions are indistinct (11;14). Behavioral recommendations and education given by physicians (the medical-behavioral or combined approach) have to be distinguished from behavioral therapy, a form of psychotherapy that employs a large number of specific techniques derived from learning theory to constructively change the patient’s behavior. The efficacy of a well described behavioral therapy combined with laxatives compared with medical treatment as recommended by the NASPGHAN (16) has never been evaluated by well-designed controlled trials.

Design

In a randomized controlled trial, 134 children aged 4-18 years with FC were randomly assigned to 22 weeks (12 visits) of either behavioral therapy or conventional treatment. Inclusion took place between November 2002 and August 2004 with the largest group of children aged 4-8 years (N= 99). Primary outcomes were defecation frequency, fecal incontinence frequency and success rate. Secondary outcomes were stool-withholding behavior and behavior problems. Outcomes were evaluated at end of treatment and at 6-months follow-up.
SORC model

Because no full and transparent description of a behavioral intervention program for FC exists a protocolized behavioral intervention program had to be developed before the actual RCT could be started (53). Literature about underlying theories about the development and maintenance of FC lead to a SORC model (table 2) from which the treatment techniques follow (40;54-57). Children show conditioned avoidance behavior (i.e. stool-withholding behavior), because of previous painful and/or fearful defecation experiences, and this behavior is maintained by its consequences (i.e. avoidance of pain) resulting in FC. Based on this SORC model a protocolized behavioral intervention program for treating childhood constipation was developed with two age-related modules (4-8 years; 8≥ years). In the module for children of 8 years and older the systematic desensitization to reduce fear is left out in the treatment, because the consequences are assumed to play a larger role in the maintenance of the constipation than pain (as antecedent and consequent). In this thesis in Chapter 2 a full and transparent description of a protocolized behavioral intervention program based on literature is presented that can serve as an extensive guideline in routine practice to treat children with FC. Chapter 3 reports the results of the efficacy of this protocolized behavioral therapy with laxatives compared with conventional treatment.

Health-Related Quality of Life, Behavior Problems and Parental Child-Rearing Attitudes

The secondary aim of this study was to investigate health-related quality of life (HRQoL), emotional and behavior problems (in this thesis for convenience shortened to behavior problems), and child-rearing which are presumed consequences of FC in the SORC model that is used in this thesis to explain FC. Exploring factors of the SORC model and their association with (clinical characteristics of) FC leads to a better insight in the mechanisms underlying FC and will finally lead to the development of effective treatment strategies. The SORC model was used as a biopsychosocial research model from which the research questions were derived:

1. How is the HRQoL of children with FC, and are clinical characteristics of FC associated with reported HRQoL?
2. What is the prevalence of emotional and behavior problems in children with FC, and are clinical characteristics of FC associated with reported emotional and behavior problems?
3. Are parental child-rearing attitudes associated with FC?
Table 2. Part 1 of 2: SORC model from which with treatment techniques and research questions were derived. Responses and consequences are cumulative.

<table>
<thead>
<tr>
<th>Model</th>
<th>S</th>
<th>O</th>
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<tr>
<td>0</td>
<td>Urg for defecation</td>
<td>Developmental mature</td>
<td>Relaxation of external anal sphincter (EAS)</td>
<td>+C+: Proper defecation, positive reactions of parents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+C-: Incomplete/no evacuation leading to hard stools</td>
</tr>
<tr>
<td>1A</td>
<td>Urg for defecation</td>
<td>Perceived stress through life events, traumatic experiences, other stressors, attention problems</td>
<td>Diminished relaxation of EAS, diminished attention for distention cues</td>
<td>-C-: Painful bowel movement, startle -C: Inhibition of relaxation of EAS, incomplete evacuation</td>
</tr>
<tr>
<td>1B</td>
<td>Urg for defecation</td>
<td>Infectious disease (dehydration), dietary transition (i.e. breast to cow milk), use of drugs, genetic disposition, which may result in hard stools</td>
<td>Relaxation of EAS</td>
<td>-C-: Painful bowel movement, startle -C: Inhibition of relaxation of EAS, incomplete evacuation</td>
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<tr>
<td>2</td>
<td>Urg for defecation</td>
<td>Disposition for fear consolidation, developmental stage, temperament</td>
<td>CER: Fear for pain CAR: Stool-withholding behavior, and stool-toileting refusal, diminished relaxation of EAS, ignoring distention cues</td>
<td>-C-: No painful bowel movement, no obstruction of play</td>
</tr>
<tr>
<td>3</td>
<td>Urg for defecation</td>
<td>Megacolon with corresponding diminished urge for defecation and accumulation of a large fecal mass</td>
<td>+C-: Involuntary fecal incontinence (FI), abdominal pain, urinary incontinence, negative reactions of parents or punishment for FI and toileting refusal, forcing of parents of proper toileting behavior, medical treatment, laxative use +C+: Positive reactions of parents on illness and illness behavior</td>
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Table 2. Part 2 of 2: SORC model from which treatment techniques and research questions were derived. Responses and consequences are cumulative.

<table>
<thead>
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<tr>
<td>4</td>
<td>Urge for defecation and stimuli associated with toileting or defecation (CS1)</td>
<td>Stimulation generalization and UCS inflation</td>
<td>CER: Fear for punishment or loss of love of parents, feelings of shame for fecal incontinence</td>
<td>+C-: Parent-child interaction problems, emotional and behavior problems, low self esteem, social consequences (i.e., sham, fewer friends, bullying)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>CAR: Hiding dirty underwear, deception about fecal accidents, denial of fecal accidents, hiding while defecating or while withholding stools</td>
<td></td>
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<tr>
<td>5</td>
<td>Anticipation anxiety or a continuous stress state of the child (CS3) because urge for defecation and stimuli associated with toileting or defecation become associated with the meaningful reinforcers</td>
<td></td>
<td>CER: Feelings of loss of control, guilt and inferiority</td>
<td>CAR: Denial of defecation problem, passivity, social isolation</td>
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UCS indicates Unconditioned Stimulus; CS indicates Conditioned Stimulus; CS1, CS2, CS3 respectively indicate the first, second and third Conditioned Stimulus; CER indicates Conditioned Emotional Response; CAR indicates Conditioned Avoidance Response; +C+ indicates the addition of a positive consequence; +C- indicates the addition of a negative consequence; -C+ indicates the removal of a positive consequence; -C- indicates the removal of a negative consequence.
**Theoretical background: Health-Related Quality of Life**

In the last decade, quality of life (QoL) is clearly established as an important separate outcome measure in medical care next to biochemical and physiological parameters (58;59). The term health related quality of life (HRQoL) narrows QoL to aspects relevant to health and encompasses a personal judgment over the physical, social and emotional effects of health disorders (60;61). Evaluating HRQoL in constipated children can help both the child and the pediatrician to recognize and address the possible impact of chronic conditions and to decide on optimal treatment strategies in order to achieve higher levels of well-being. Furthermore, on group level HRQoL is increasingly recognized as an outcome measure in pediatric treatment evaluations (62).

FC with secondary fecal incontinence is a chronic condition that often is a source of distress and concern for a child. Chronic symptoms of FC in children are associated with a lower health related quality of life (HRQoL), as measured with generic questionnaires (63). Whether specific disease characteristics, such as fecal incontinence, explain this lower HRQoL is better measured with a disease specific instrument than with a generic instrument. Disease-specific instruments include domains designed to be valid only for specific patient populations, as they assess disease-related aspects of HRQoL (58). Furthermore, disease-specific instruments are more responsive to disease specific factors that have an impact on HRQoL. Contrary to generic instruments, comparison of HRQoL between different patient populations and normative data from healthy populations is not possible. Previously, a disease specific instrument was developed to assess the impact of FC and fecal incontinence on HRQoL in children; the Defecation Disorder List (64). In a small group of 27 patients good reliability and test-retest stability was found, making the DDL a promising tool for measurement of disease specific HRQoL. In **Chapter 4**, the HRQoL in children with constipation-associated fecal incontinence is described in association with clinical characteristics. In addition, the applicability of the DDL was further tested in this cohort of children with constipation-associated fecal incontinence.

**Theoretical background: Behavior Problems**

FC is often associated with emotional and behavior problems (32;45-48). Early literature suggested that fecal incontinence is a mental disorder that requires psychiatric treatment (65;66). However, several intervention studies showed an association between successful treatment of FC and fecal incontinence, and the reduction of behavior problems suggesting that behavior problems are secondary (32;33;49;50). To date the question whether behavior problems result in constipation or vice versa is a major point of controversy and still not answered. **Chapter 5** assesses the prevalence of overall, internalizing and externalizing behavior problems in children with FC, and explores which clinical characteristics of constipation are associated with these emotional and behavior problems.

**Theoretical background: Parental Child-Rearing Attitudes**

Parental reactions are assumed to contribute to constipation in the child; however, the influence of parental factors on FC has received minor attention in the research field. Parents report more aversive parenting around toileting related to incompliance by the child to use the toilet and deception concerning fecal accidents (13). Parenting constipated children may be more challenging because of more stubbornness (67), difficult temperament (68-70) and emotional and behavior problems in these children (32;45-48). However, knowledge about
the association between parenting factors and childhood constipation is limited. Chapter 6 investigates the association between parental child-rearing attitudes and FC outcomes while correcting for emotional and behavior problems.

**Design**

The studies investigating behavior problems and parental child-rearing attitudes made use from baseline data of 133 children aged 4-18 years participating in the randomized controlled trial evaluating the efficacy of behavioral therapy compared with conventional treatment. Inclusion took place between November 2002 and August 2004 with the largest group of children aged 4-8 years (N=98). Inclusion for the study on HRQoL took place between September 2001 and November 2005. This study investigated 136 children aged 8-18 years. The sample includes children that participated in our RCT study evaluating the efficacy of behavioral therapy (N= 35), and children that participated in a separate RCT study evaluating the efficacy of use of rectal enemas in children with severe constipation (symptoms for at least two years and unresponsive to medical treatment; N=101) (71).

In Chapter 7, the findings described in the previous chapters are summarized and discussed. Then limitations of the studies are addressed, and implications for clinical practice and future research are presented.
References


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