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Brain processing of rectal sensation in adolescents with functional defecation disorders and healthy controls

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Abstract

Background: Decreased sensation of urge to defecate is often reported by children with functional constipation (FC) and functional nonretentive fecal incontinence (FNRFI). The aim of this cross-sectional study was to evaluate cerebral activity in response to rectal distension in adolescents with FC and FNRFI compared with healthy controls (HCs).

Methods: We included 15 adolescents with FC, 10 adolescents with FNRFI, and 15 young adult HCs. Rectal barostat was performed prior to functional magnetic resonance imaging (fMRI) to determine individual pressure thresholds for urge sensation. Subjects received 2 sessions of 5 × 30 seconds of barostat stimulation during the acquisition of blood oxygenation level-dependent fMRI. Functional magnetic resonance imaging signal differences were analyzed using SPM8 in Matlab.

Key Results: Functional constipation and FNRFI patients had higher thresholds for urgency than HCs ($P < .001$). During rectal distension, FC patients showed activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, inferior parietal lobule, and putamen. No activations were observed in controls and FNRFI patients. Functional nonretentive fecal incontinence patients showed deactivation in the hippocampus, parahippocampal gyrus, fusiform gyrus (FFG), lingual gyrus, posterior parietal cortex, and precentral gyrus. In HCs, deactivated areas were detected in the hippocampus, amygdala, FFG, insula, thalamus, precuneus, and primary somatosensory cortex. In contrast, no regions with significant deactivation were detected in FC patients.

Conclusions & Inferences: Children with FC differ from children with FNRFI and HCs with respect to patterns of cerebral activation and deactivation during rectal distension. Functional nonretentive fecal incontinence patients seem to resemble HCs when it comes to brain processing of rectal distension.

KEYWORDS

adolescents, children, constipation, fecal incontinence, fMRI

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention deficit hyperactivity disorder; AVL, Dutch ADHD questionnaire (*ADHD vragenlijst*); BOLD, blood oxygenation level dependent; CTT, colonic transit time; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional constipation; FDD, functional defecation disorder; FFG, fusiform gyrus; fMRI, functional magnetic resonance imaging; FNRFI, functional nonretentive fecal incontinence; FOV, field of view; HC, healthy control; IBS, irritable bowel syndrome; IPL, inferior parietal lobule; IQR, interquartile range; MDP, minimal distension pressure; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; SCARED-NL, Screen for Child Anxiety Related Emotional Disorders—Dutch version; TE, echo time; TR, repetition time.

1 | INTRODUCTION

Functional defecation disorders (FDDs) in children over 4 years of age comprise functional constipation (FC) and functional nonretentive fecal incontinence (FNRFI), which are diagnosed according to the symptom-based Rome IV criteria.[1] Both disorders are characterized by bothersome symptoms (eg, fecal incontinence), which often result in a decreased quality of life.[2,3] These symptoms can be difficult to treat and may even persist into adolescence and adulthood if therapeutic management is unsuccessful.[4] The pathophysiology of both FC and FNRFI is incompletely understood.

Although both disorders are often characterized by fecal incontinence,[5] they are recognized as different clinical entities.[1] In children with FC, the involuntary loss of stool is considered to be the consequence of overflow incontinence due to fecal impaction in the rectum, which is often the result of excessive stool withholding behavior. The preferred treatment for these patients consists of behavioral interventions (eg, toilet training with a reward system) and laxative drugs.[6] In FNRFI, it is hypothesized that children neglect or ignore the urge to defecate.[7] Furthermore, coexisting psychological comorbidities are common in this population and may also play a role in the pathophysiology.[8] Treatment of FNRFI also consists of behavioral interventions, while the use of laxative drugs is discouraged in these patients as this may worsen symptoms.[8]

Many children with FC and FNRFI report that they lack the sensation of urge to defecate, which may contribute to the involuntary loss of stool seen in both patient groups. Impaired peripheral rectal sensitivity has therefore been postulated as a potential common underlying pathophysiological mechanism in FDDs. This lack of sensation is incompletely understood, but may be related to abnormalities in the brain-gut axis. It is now well known that bidirectional brain-gut interactions are important in the regulation of digestive processes, including the regulation of bowel movements.[9] Sensations arising from the gastrointestinal tract, such as the urge to defecate or visceral pain, are transported from the enteric nervous system, via the spinal cord to the cerebral cortex. Abnormal processing of sensory signals can occur at any level in this neural pathway, from the mechanoreceptors in the gut wall to the brain centers processing the afferent information.[10] This central processing may be impaired in children with FDDs who report a loss of urge sensation.

The importance of brain-gut interactions in functional gastrointestinal disorders (FGIDs) is increasingly recognized and most prominently studied in patients with irritable bowel syndrome (IBS) by using functional magnetic resonance imaging (fMRI).[11,12] This technique measures changes in the ratio of deoxyhemoglobin to oxyhemoglobin (the blood oxygen level-dependent [BOLD] signal) in the brain. If a rectal barostat investigation is performed during a BOLD fMRI, this technique provides information on changes in brain activity in response to (visceral) stimuli.[11,13] Activation and deactivation of multiple cortical regions have been shown to be associated with rectal distension in patients with IBS.[14,15] The most consistently activated brain regions during visceral distension are known to support emotional arousal, processing of visceral afferent information, and cognitive modulation, including the insula, the anterior cingulate cortex (ACC), the primary sensory cortex, prefrontal cortex (PFC) regions, and the thalamus.[16-18] Although fMRI studies have been performed in adults with IBS before,[14,15] fMRI studies in patients with FDDs are rare. In a recently published study among adults with FC and healthy controls (HCs), Zhu et al. found significant differences in baseline brain activity in a number of major brain regions implicated in emotional process modulation, somatic and sensory processing, and motor control.[19] To date, fMRI data of children with FDDs have not been published.

We hypothesized that the loss of rectal sensation in children with FDDs is related to impaired brain processing of visceral sensory stimuli, which may result in fecal incontinence. Therefore, the aim of this study was to compare the cerebral activity in response to rectal distension in adolescents with FC and FNRFI and compare this with HCs.

Key Points

- Children with FC and FNRFI often report a lack of urge sensation, which may contribute to the involuntary loss of stools in these children.
- In this study, we performed fMRI during rectal distension with barostat and found that children with FC differ from children with FNRFI and healthy controls with respect to patterns of cerebral activation and deactivation during rectal distension.
- These findings suggest different neural processing of rectal distension and confirm that FNRFI is a different clinical entity than FC.

2 | MATERIALS AND METHODS

2.1 | Study subjects

Fifteen patients with FC (age range 12-18 years), 10 patients with FNRFI (age range 12-18 years), and 15 healthy young-adult controls (age range 18-21 years) participated in this study. Patients were recruited between February 2011 and September 2013 from the outpatient clinic of the department of pediatric gastroenterology at our tertiary referral center. Patients were included if they fulfilled the Rome III criteria for FC or FNRFI for a duration of at least 2 years.[20] Exclusion criteria were as follows: (i) organic causes of constipation, including Hirschsprung's disease, spina bifida, mental retardation, or hypothyroidism; (ii) prior anorectal surgery; (iii) intercurrent illness or active colitis; (iv) known allergy to latex or polyethylene; (v) incapability to verbally communicate and cooperate; or (vi) claustrophobia. Healthy controls were recruited through local advertisements and were not eligible to participate if they had gastrointestinal symptoms or a history thereof, the same exclusion criteria listed for pediatric patients applied to HCs. All participants underwent a basic medical

history and physical examination to see if they met the general eligibility criteria to undergo an MRI.

2.2 | Questionnaires

A standardized questionnaire was used to evaluate defecation symptoms. All study subjects were screened for anxiety and attention deficit hyperactivity disorder (ADHD) symptoms, because it is known that enhanced attention and anxiety influences fMRI findings in adults with FGIDs.[21,22] These symptoms were measured with the Dutch version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-NL) and a Dutch ADHD questionnaire (AVL).[23,24] The Dutch version of the State Trait Anxiety Index and the Adults Self-Repost Scale were used in the HCs.[24,25]

2.3 | Colonic transit time

Colonic transit time (CTT) was measured in all adolescents with FDDs. A single abdominal X-ray was taken after daily ingestion of capsules, each containing 10 radiopaque markers, on 6 consecutive days. Cutoff values for normal CTTs were 18, 20, 34, and 62 hours for the right colon, left colon, rectosigmoid, and total colon, respectively. Colonic transit time results were utilized to confirm the diagnosis of FNRFI. In these patients, a normal CTT confirms the diagnosis of FNRFI.[8,26] A patient with FC and a total colonic time of more than 62 hours was considered to have slow transit constipation.[27]

2.4 | Barostat data acquisition

All subjects used an enema prior to the barostat test to empty the rectum. All other medications known to affect gastrointestinal motility were discontinued 48 hours prior to the barostat procedure. Prior to the study inside the MRI scanner, a standardized rectal barostat test was performed outside of the MRI scanner to determine individual sensitivity thresholds. We used a lubricated noncompliant polyethylene balloon with a maximum volume of 500 mL and a maximum diameter of 10 cm, which was introduced into the rectum. The barostat pump (Distender II; G&J Electronics Inc, Toronto, Ontario, Canada) was connected to a catheter with a length of 11 m, allowing the pump to be in the control room away from the MRI magnet. After rectal insertion, the balloon was unfolded stepwise (30 mL per step) to a maximum volume of 150 mL, and then the catheter was pulled back against the pelvic floor. The minimal distension pressure (MDP) was defined as the pressure resulting in an intraballoon volume of at least 30 mL, and determined by a stepwise increase in the intraballoon pressure (in 1 mm Hg steps lasting 1 minute). Thresholds for rectal sensitivity to distension were evaluated using intermittent distension with steps of 3 mm Hg lasting 1 minute and 1-minute resting intervals at MDP between steps. At every pressure step, the patient was asked to score sensation, using an ordinal scale ranging from 0 to 5 (0 = no sensation, 1 = first sensation, 2 = urge to defecate, 3 = moderate urge to defecate, 4 = severe urge to defecate, 5 = pain). When pain occurred, the balloon was deflated immediately and the study was ended.

2.5 | Functional MRI data acquisition

After the barostat study and a resting period of at least 5 minutes, subjects were positioned inside the MRI scanner and were instructed to remain still for the duration of the procedure. The subjects were given earplugs to reduce scanner noise and a speaker and microphone allowed 2-way communication with the experimenters. Rectal distension-induced brain activation and deactivation were measured with fMRI using distension pressures at the individual level of urge to defecate in the adolescent FDD patients and severe urge to defecate in the healthy adults, as determined during the prior barostat study. This difference was based on ethical considerations, we wanted to avoid a painful experience in all subjects who volunteered to participate in this study and therefore chose for a level of distension inducing urge of defecation. However, as we included a pediatric patient population and as these children already have negative experiences related to defecation, we wanted to avoid noxious stimuli to the best of our ability and therefore opted for a less bothersome level of urge of defecation compared to the HCs. In patients who did not perceive urge to defecate during the barostat study, we used the maximum pressure of MDP +24 mm Hg, based on thresholds for sensation in previous barostat studies.[28] The baseline pressure during the rest periods was set at MDP to prevent balloon collapse. Functional and structural images were acquired during rectal distension on a 3-Tesla MRI scanner (Intera; Philips Healthcare, Best, The Netherlands) equipped with an 8-channel SENSE head receive coil. A T2*-weighted echo planar imaging sequence was acquired with the following parameters: repetition time (TR) = 3000 millisecond, echo time (TE) = 30 millisecond, flip angle = 90°, SENSE factor 2.5, 112 × 109 matrix, field of view (FOV) = 220 × 220 × 131.7 mm, slice thickness = 3.0 mm, slice gap = 0.3 mm, voxel size = 1.72 × 1.72 × 3 mm, with 40 axial slices, in ascending mode covering the whole brain. In addition, a structural T1-weighted 3D anatomical image of the whole brain was obtained (TR = 9 millisecond, TE = 3.6 millisecond, SENSE-factor = 2.5, 256 × 255 matrix, FOV = 256 × 256 × 180 mm, 100 slices, reconstructed voxel size = 0.5 × 0.5 × 1 mm, sagittal slice orientation).

For the fMRI study, a block design was implemented in 2 runs in which phases of distension alternated with phases without distension. Each run consisted of 5 repetitions of 30 seconds of rectal stimulation, followed by 30 seconds of rest (Figure 1). There was a lag time of 7 seconds before reaching the first peak pressure after initiation of the stimuli.

2.6 | Data analysis

Thresholds for sensation were determined from the intermittent distension protocol and expressed as pressure above MDP. Subjects were considered hyposensitive if they required a pressure >19 mm Hg above MDP to induce an urge to defecate, this cutoff value was based on a previous study in 22 healthy children (8-16 years).[28]

Baseline patient data are expressed as percentages, medians, and interquartile ranges (IQR). Because of data distribution and sample size, nonparametric tests (Kruskal-Wallis test) were used for comparing

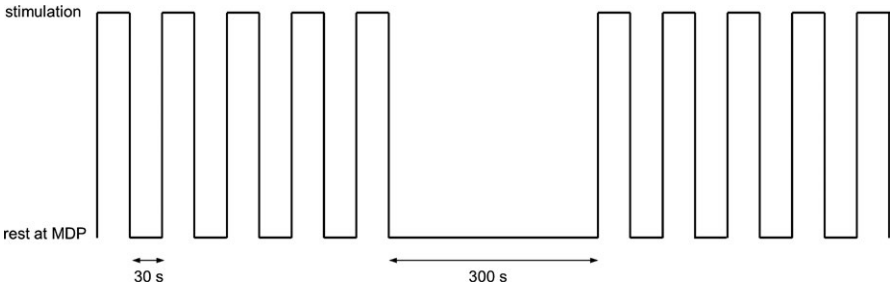

FIGURE 1 The block design used during fMRI scans; 2 runs of 5 repetitions of 30 seconds of rectal stimulation, followed by 30 seconds of rest

sensation thresholds. Significance was considered at $P < .05$. For the post hoc analyses, nonparametric tests (Mann-Whitney *U* test) were used after Bonferroni correction ($P < .025$).

For fMRI data analysis, SPM8 toolbox for Matlab (Natick, Massachusetts, USA) version 7.14 was used. Prior to statistical analysis, images were preprocessed by realignment to the first scan to correct for interscan movement artifacts, normalized to the Montreal Neurological Institute (MNI) template, and spatially smoothed with a Gaussian filter (FWHM = 8 mm). Images were excluded from further analysis if the realignment parameters indicated excessive interscan movement (>0.6 mm). A first-level general linear model was specified for each subject using the previous defined block design (Figure 1), with a delay of 7 seconds. The computed contrasts for the second-level (random effects) analysis were the differences between stimulation and rest periods. We initially assessed the effect of stimulation within the groups and subsequently assessed intergroup differences. Cerebral activation was defined as BOLD increase during rectal distension vs rest and cerebral deactivation as BOLD decrease during rectal distension vs rest. Activation maps were inspected at a statistical threshold of $P < .001$, which protects against type I errors when cluster-based thresholding is applied.[29] Activated clusters that survived a cluster-based correction for multiple comparisons at $P < .05$ were considered statistically significant. Furthermore, regions of interest based on MNI coordinates published in a meta-analysis[11] were used to restrict the search volume (small volume correction using a 10 mL sphere and FWE correction). Group differences were masked with group averages of task activation and deactivation to test for the specificity of statistical effects.

2.7 | Ethical considerations

The study protocol was approved by the medical ethics committee of the Academic Medical Center and all subjects (and their parents if the subjects were <18 years of age) gave written informed consent prior to the study. All authors had access to the study data and reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Subject characteristics

Subject characteristics and barostat data are shown in Table 1. In the FC group, 47% of patients presented with fecal incontinence and 93% reported to have a lack of urge sensation in daily life. In the FNRFI group, 50% reported to have a lack of urge sensation in daily life. All FC patients had an extensive history of medication use, including laxatives, enemas, and oral or rectal colonic lavage regimens. In the FC group, 13 patients (87%) had a delayed CTT; 8/13 patients fulfilled the criteria for slow transit constipation and 5/13 had outlet obstruction.[27] The remaining 2 FC patients had a normal CTT, but in these patients, the test was performed while using laxative medication. All adolescents in the FNRFI group had a normal CTT. Anxiety scores were within the normal range for all subjects. Based on the ADHD screening questionnaire, 1 FC patient and 1 HC had clinically relevant ADHD scores. These patients were not diagnosed with ADHD prior to enrollment in the study and did not report problems that were attributable to ADHD, therefore, after consulting our psychology department, these patients were not referred for further evaluation.

3.2 | Rectal distension thresholds

Rectal stimulation with the barostat and the fMRI study were well-tolerated by all subjects. There were no significant differences between the 3 groups regarding the MDP or the threshold for first sensation (Table 1). However, FDD patients exhibited significantly higher thresholds for urge sensation than HCs (Table 1); FC patients required a median pressure of 18.0 mm Hg above MDP to provoke urge sensation, this was 13.5 mm Hg for FNRFI patients and of 9.0 mm Hg above MDP in HCs.

In the FC group, 7 patients were considered to be hyposensitive; the pressure threshold for urge to defecate was >19 mm Hg above MDP. According to this definition, 2 FNRFI patients and none of the HCs were hyposensitive. Four FC patients never experienced the sensation of urge during rectal distension, and the maximal stimulation of 24 mm Hg above MDP was used during the fMRI scans. In the HC group, we used the individually determined threshold for severe urge to defecate to evaluate brain activity, which was at a median pressure of 33 mm Hg above MDP (IQR 27.0-36.0).

3.3 | Brain response to rectal distension

The study groups differed with regard to the activated and deactivated regions in response to rectal distension. Patients with FC showed BOLD increases (activation) in the ACC, bilateral dorsolateral prefrontal cortex (DLPFC), right inferior parietal lobule (IPL), and putamen

TABLE 1 Subjects' characteristics and barostat data

	FC	FNRFI	HC	*P*-value
Age in years (IQR, range)[1]	14.0 (12.0-16.0, 12-18)	13.0 (12.0-15.25, 12-17)	20.0 (20.0-21.0, 18-21)	.000[a,i]
Sex (% male)	53%	80%	40%	.142[b]
Defecation frequency, per week (IQR, range)[1]	1.0 (0.5-3.0, 0-5)	4.0 (3.375-7.0, 3-14)	7.0 (4.5-12, 2.5-20)	.000[a,ii]
Fecal incontinence	47%	100%	-	.005[b]
Fecal incontinence, per week (IQR, range)[1]	3.0 (1.0-7.0, 0.5-7)	4.5 (1.875-11.0, 1-15)	-	.230[c]
Urge sensation abnormal	93%	50%	-	.038[b]
Urinary incontinence	13%	33%	-	.243[b]
Age start symptoms, years (IQR, range)[1]	4.0 (1.0-13.0, 0.5-16)	4.75 (3.75-6.25, 3-7)	-	.791[c]
Duration of symptoms, years (IQR, range)[1]	9.0 (2.0-12.5, 1-17.5)	8.75 (7.75-9.25, 7-10)	-	.910[c]
Colonic transit time, hours (IQR, range)[1]	90 (81-124, 62-144)	45 (33-53, 21-57)	-	.000[c,d]
MDP mm Hg (IQR, range)[1]	7.0 (6.0-11.0, 4-14)	6.5 (6.0-11.3, 4-13)	5.0 (3.0-9.0, 3-11)	.151[a]
First sensation mm Hg >MDP (IQR, range)[1]	6.0 (3.0-6.0, 3-24)	6.0 (3.0-9.0, 3-9)	3.0 (3.0-6.0, 3-6)	.392[a]
Urge mm Hg >MDP (IQR, range)[1]	18.0 (12.0-24.0, 9-24)	13.5 (12.0-18.8, 6-22)	9.0 (6.0-9.0, 3-18)	.000[a,iii]

[1]Results are depicted as median. [a]Kruskal-Wallis test, sign <.05. [b]Pearson's chi-squared, sign <.05. [c]Mann-Whitney test, sign <.05. [d]Only CTT's of patients without medication were used in this analysis: 10/15 FC patients, 10/10 FNRFI patients. [e]Mann-Whitney test after Bonferroni correction (sign <.025); [i]FC vs FNRFI no significant difference (.643[e]). Both FC and FNRFI significantly differ from HC (.000[e] and .000[e]). [ii]FNRFI vs HC no significant difference (.144[e]). Both FNRFI and HC significantly differ from FC (.001[e] and .000[e]). [iii]FC vs FNRFI no significant difference (.115[e]). Both FC and FNRFI significantly differ from HC (.000[e] and .001[e]).

during rectal distension compared to rest periods. No BOLD increases were observed in controls or FNRFI patients during rectal distension periods. To verify whether we might have missed a transient response to rectal distension in the controls, we separately modeled the first 15 seconds of the 30 seconds distension period and contrasted it with the rest period but no BOLD increases were observed in this contrast either. These observations were confirmed by group comparisons that showed stronger activations in these areas in FC patients vs HCs and FNRFI patients (Table 2, Figure 2).

Extensive deactivated areas were detected in FNRFI patients and HCs during rectal distension vs rest (higher BOLD activation during rest than distension). FNRFI patients showed significant deactivation in the hippocampus, parahippocampal gyrus, fusiform gyrus (FFG), lingual gyrus, posterior parietal cortex, and precentral gyrus. In HCs, significantly deactivated clusters included the bilateral hippocampus, amygdala, FFG, posterior insular cortex, thalamus, precuneus, and primary somatosensory cortex. In contrast, no regions with significant deactivation in response to rectal distension were detected in FC patients (Table 3, Figure 2). *Z*-scores indicated that the degree of deactivation was smaller in FNRFI patients compared to HCs. Again, these observations were confirmed by group comparisons that showed a lesser extent of deactivation in FC patients compared to HCs. The FC patients did not show a lesser extent of deactivation than the FNRFI patients in the group analysis.

4 | DISCUSSION

In our study, barostat testing revealed an impaired urge sensation in adolescents with FDDs compared to HCs. Furthermore, the cerebral response to rectal distension of adolescents with FC significantly differed from that of HCs. In contrast, the cerebral response in adolescents with FNRFI resembled that of HCs. FNRFI patients seemed to have a distinctly different pattern of activation and deactivation during rectal distension than FC patients, but these latter differences were not significant.

TABLE 2 Brain areas activated (distension > rest) during rectal distension

Region	BA	x^a	y^a	z^a	*Z*-value	*P*-value
FC patients						
aMCC/ACC	24/32	−9	14	40	4.03	.006
L DLPFC	46	−33	44	19	3.58	.028
R DLPFC	46	30	44	34	3.57	.024
R IPL	40	57	−34	40	3.81	ns
L putamen	X	−30	5	7	3.44	.035
R putamen	X	21	−5	4	3.33	.048
FNRFI patients						
No significant clusters						
Healthy controls						
No significant clusters						
FC patients > HCs						
aMCC/ACC	34/32	−9	14	40	3.86	.01
R DLPFC	46	33	44	28	3.2	.067
IPL	40	60	−34	43	3.59	ns
FC patients < HCs						
No significant clusters						
FNRFI patients > Controls						
No significant clusters						
FNRFI patients < Controls						
No significant clusters						
FC patients > FNRFI patients						
R DLPFC	46	33	44	28	3.15	.08
R IPL	40	57	−31	43	3.58	ns
FC patients < FNRFI patients						
No significant clusters						

BA, Broadmann area; L, left; R, right; aMCC, anterior midcingulate cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule.
[a]MNI coordinates.

4.1 | Barostat

The level of pressure that was required to induce an urge sensation, was significantly higher in adolescents with FC and FNRFI compared to HCs. This corroborates our hypothesis that impaired rectal sensation may play a role in the pathophysiology of FC and FNRFI. The pathophysiological mechanism underlying this impaired rectal sensation remains to be elucidated. Rectal compliance has been suggested to potentially play a role in impaired rectal sensation. A previous study showed that 58% of children with FC had an increased rectal compliance, however, in that study no statistically significant differences in rectal sensitivity thresholds were identified between children with FC, FNRFI, and HCs.[30] Visceral sensation may be initiated by wall tension, pressure, or volume receptors.[31] It is unknown if long-term fecal impaction leads to impaired sensation of visceral sensory stimuli. It could be hypothesized that prolonged fecal stasis in the rectum may result in dilatation, altered distensibility of the rectal wall, and an increased rectal compliance. To date, evidence on the role of rectal compliance in pediatric FDDs is ambiguous. Although a higher rectal compliance was found in FC patients compared to FNRFI patients and healthy volunteers,[30] the relation with clinical outcome is unclear as patients with FC can be in clinical remission despite having an increased rectal compliance and an increased rectal compliance is not related to treatment failure.[28,32] In the current study, we did not measure rectal compliance because the primary aim of this study was to evaluate cerebral responses to visceral sensations. Therefore, we used a different barostat protocol in order to reduce the time that subjects were under investigation with barostat and MRI.

4.2 | Activations

In this study, FC patients showed activation of the ACC, bilateral DLPFC, right IPL, and putamen during rectal distension compared to resting. No significant activated regions were found in the FNRFI patients or HCs. In previous studies in adult IBS patients and healthy adults, activations in the ACC, PFC regions, and putamen have also been observed. This has been considered to be associated with a disturbed pain sensation. However, activation of the insula, primary sensory cortex, and the thalamus, as often described in the literature, was not found in our study group.[11,16-18] The reported activated brain regions during rectal distension are involved in emotional arousal, processing of visceral afferent information, and cognitive modulation. The ACC appears to be critical for integrating sensation with memory, allowing full appreciation and evaluation of the meaningfulness of the stimulus in light of previous experience.[17,33] We speculate that activation of the ACC during rectal stimulation in FC patients is related to negative and painful experiences prior to and during defecation. Activation of this area was not found in FNRFI patients or HCs, indicating that these groups do not express an emotional response to the given stimulus.[33]

The PFC provides cognitive evaluation of visceral sensation, allowing the individual to assess its quality and judge its unpleasantness.[34] We speculate that adolescents with FC have a more active cognitive evaluation of the rectal stimulus, highlighted by a more active PFC, compared to FNRFI patients and HCs. This could reflect that on a cerebral level, adolescents with FC are aware of their rectal sensations and that abnormal cognitive modulations occur in response to rectal distension, whereas this does not occur in adolescents with FNRFI.

Several hypotheses may explain the lack of observed activations in FNRFI patients and HCs. The given rectal stimulus in this study might not have been strong (intense) enough, as we did not continue rectal distension up to the point of pain sensation in any of the subject groups due to ethical considerations. Instead, we inflated the rectal barostat balloon to the level of urge sensation to defecate in the adolescent FDD patients and to the point of severe urge to defecate in HCs. Silverman et al. found a lack of activation within the ACC

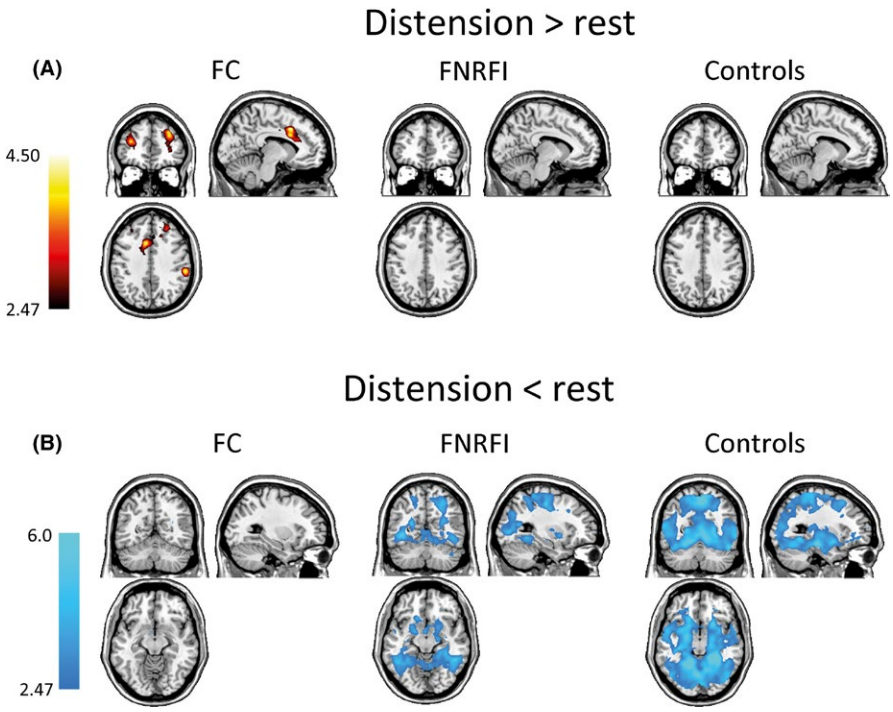

FIGURE 2 A, Regions showing cerebral activation (distension > rest) in FC patients, FNRFI patients, and HCs during rectal distension. Color bar indicates statistical *T* values. B, Regions showing cerebral deactivation (distension < rest)

and PFC during nonpainful stimuli in healthy subjects.[17] Mertz et al. also observed that only pain led to a greater activation of the ACC.[13] Therefore, administration of a painful stimulus in our subject groups, rather than a stimulus of urge, could potentially have resulted in different results. However, in our study both FDD patient groups received the same stimuli, so the different trends that were found between patients with FC and FNRFI cannot be attributed to a difference in stimulus.

4.3 | Deactivations

In contrast to adolescents with FC, extensive deactivated areas were detected during rectal distension vs rest in FNRFI patients and HCs. Significantly deactivated clusters included the hippocampus, parahippocampal gyrus, FFG, lingual gyrus, posterior parietal cortex, and precentral gyrus in FNRFI patients and the hippocampus, amygdala, FFG, posterior insular cortex, thalamus, precuneus, and primary somatosensory cortex in HCs. Reports have traditionally focused on increased BOLD signals, corresponding to regional brain activation, but there is increasing recognition of the importance of deactivations.[35] Deactivated regions that were observed in this study are consistent with previous adult studies of response to rectal stimulation, suggesting that these areas often function together in processing visceral stimuli.[17,33,35-40]

The thalamus, hippocampus, and insula are regions of the homeostatic afferent network, which is important for behavioral, spatial, and memory functions.[33] The insula is an important area for integration of visceral and somatosensory input and plays a role in coordinating a viscerosomatic autonomic response to pain.[10,34] These regions were also deactivated in the study by Song et al., they suggested that mental attention focused away from the averse stimulus (or distraction) leads to diminishing of the stimulus and to downregulation of activation in the insula and thalamus.[41] This could be considered as a coping mechanism of the brain to endure an unpleasant stimulus. Deactivations have also been described before during esophageal distension and have been explained as attentional processes, explicated as a process of "filtering out other sensory processing."[34] Our observations could be interpreted in a way that supports this theory. One could hypothesize that FNRFI patients and HCs might have been more distracted by the fMRI scan compared to FC patients and that they were possibly better able to divert attention away from rectal stimulation.

Deactivations were also found in the hippocampus and amygdala, which are sensory regions that are mainly involved in processing exteroceptive information. The amygdala is part of the limbic system and performs a primary role in the processing of memory and emotional reactions, especially fear.[42] Deactivation of the amygdala may represent an adaptive response to an unavoidable noxious stimulus.[36] In our study, the subjects were aware of the intensity and duration of the stimulus they would endure; therefore, it can be hypothesized that they developed a coping strategy to tolerate this uncomfortable sensation.[34,37,40]

In a study by Berman et al., deactivations were observed in the insula, amygdala, and thalamus in response to rectal distension in both healthy men and women.[40] It was demonstrated that subjects with the least anxiety had the greatest decreases. There is a well-recognized association between emotional and social factors and gut function. In particular, patients with constipation tend to have higher scores on scales of somatization, interpersonal sensitivity, anxiety, and depression.[43] Although anxiety disorders were excluded in both of our study groups, FC patients might have been more anxious for the stimulus during the fMRI scan, leading to less deactivation in the above-mentioned regions. These interpretations are in line with investigations in cognitive

TABLE 3 Brain areas deactivated (distension < rest) during rectal distension

Region	BA	x^a	y^a	z^a	*Z*-value	*P*-value
FC patients						
No significant clusters						
FNRFI patients						
L HC/PHG/FFG/lingual gyrus	37	−45	−49	−5	4.8	<.001
R HC/PHG/FFG/lingual gyrus	37	45	−49	−8	4.72	<.001
R PPC	X	24	−43	49	4.74	<.001
L cingulum, SMA, precentral gyrus	6	−24	−16	46	4.64	<.001
R SMA/precentral gyrus	6	15	−4	58	4.6	<.001
Healthy controls						
L HC/PHG/amygdala	20	−36	−25	−17	5.8	<.001
R HC/PHG/amygdala	20	33	−13	−23	5.22	<.001
FFG/lingual gyrus	18/19/30/37	21	−40	−11	6.25	<.001
FFG/lingual gyrus	18/19/30/37	−15	−52	−11	5.53	<.001
Posterior insula	X	33	−10	13	5.09	<.001
L thalamus	X	−15	−31	1	5.43	<.001
R thalamus	X	15	−31	4	5.71	<.001
Precuneus/primary somatosensory cortex	5,7	3	−34	67	5.07	<.001
FC patients < HCs						
L HC/PHG/amygdala	20/36	−36	−25	−17	5.37	.051
R HC/PHG/amygdala	20/36	30	−28	−17	4.62	<.001
FFG/lingual gyrus	18/19/30/37	21	−40	−11	5.34	<.001
FFG/lingual gyrus	18/19/30/37	−15	−49	−11	4.8	<.001
Posterior insula	X	33	−13	10	4.16	<.001
L thalamus	X	−15	−31	1	4.41	<.001
R thalamus	X	18	−31	1	4.62	<.001
Precuneus/primary somatosensory cortex	5/7	6	−58	55	4.87	<.001
FC patients > HCs						
No significant clusters						
FNRFI patients > Controls						
No significant clusters						
FNRFI patients < Controls						
No significant clusters						
FC patients > FNRFI patients						
No significant clusters						
FC patients < FNRFI patients						
No significant clusters						

BA, Broadmann area; L, left; R, right; HC, hippocampus; PHG, parahippocampal gyrus; FFG, fusiform gyrus.

[a]MNI coordinates.

neuroscience of the Default Mode Network (DMN).[44,45] The DMN is a network of interacting brain regions in which activity is most commonly observed when a subject is not focused on the outside world.

4.4 | Considerations

The patients included in this study represent a group of patients with severe FDDs; they suffered from long-standing problems, they had high thresholds for urge to defecate, and had significantly delayed CTTs. The majority of FC patients reported to have an impaired urge sensation in daily life. Based on our results, one could hypothesize that the impaired rectal urge sensation in adolescents with FC could be due to abnormal/dysfunctional brain processing. Therefore, therapies aimed at modifying the brain-gut axis, such as hypnosis and biofeedback, might be beneficial in this subset of patients. Further studies should be conducted to investigate if these treatment options improve clinical symptoms and if brain response to rectal stimuli could be modified. On the other hand, FNRFI patients, often with similar symptoms of lack of urge sensation, have a brain processing response to rectal distension that has similarities when compared to HCs and seems to differ from FC patients. Half of patients with FNRFI reported to suffer from loss of urge sensation in daily life. The reported lack of urge does not fully corroborate the barostat data, it is questionable whether patients adequately assessed their own ability to feel urge sensation.

There are potential limitations to the interpretation and generalizability of our results that should be taken into account. During the scans the subjects were asked to remain completely still and communication was only allowed in case of emergency. This approach was chosen to prevent body movement and movement artifact on the scans. The drawback of this method is that evaluation of rectal sensation was not possible during imaging. Moreover, differences in stimulus strength between the 2 FDD groups and the HC group in this study might have contributed to some extent to the observed differences. However, it seems unlikely that differences in stimulus strength are responsible for the widespread pattern of deactivation in controls that was completely absent in patients with FC. Also, patients with FNRFI received the same individually tailored stimuli and they did show deactivation, which had overlap with the observations in HCs. Furthermore, it would have been preferable to compare our adolescent patient population with healthy adolescent controls. For ethical reasons, we decided to use an adult control group under the age of 21 for comparison.

It would have been valuable to perform supplemental analyses to investigate if there were gender and age differences in brain responses during rectal distension within the FDD groups. It would also have been interesting to evaluate whether brain responses were different between hyposensitive patients who never experience sensation of urge to defecate, compared to normosensitive patients. Unfortunately, our current sample was not sufficiently powered to test these additional hypotheses. How this would influence the current results is unknown and should be further investigated in future research. Furthermore, it would be interesting to investigate the cerebral response to rectal distension in former patients with FC who are in clinical remission and no longer require treatment.

5 | CONCLUSION

In conclusion, adolescents with FDDs often suffer from an impaired visceral sensation of urge. Adolescents with chronic FC differ from HCs with respect to patterns cerebral response to rectal distension in multiple brain regions which are involved in attentional functions as well as cognition, motor coordination, memory, emotional, and sensory association. Functional nonretentive fecal incontinence patients seem to resemble HCs when it comes to brain processing of rectal distension.

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DISCLOSURE

The authors have no potential conflicts of interest to declare with regard to this publication.

AUTHOR CONTRIBUTIONS

SMM study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; IJNK analysis and interpretation of data; drafting of the manuscript; MMvdB study concept and design; acquisition of data; drafting of the manuscript; PFCG study concept and design; critical revision of the manuscript for important intellectual content; LR study concept and design; critical revision of the manuscript for important intellectual content; MBdR study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; MAB study concept and design; critical revision of the manuscript for important intellectual content; study supervision.

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REFERENCES

1. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. *Gastroenterology*. 2016;150:1456-1468.
2. Belsey J, Greenfield S, Candy D, et al. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther*. 2010;31:938-949.
3. Silverman AH, Berlin KS, Di Lorenzo C, et al. Measuring health-related quality of life with the parental opinions of pediatric constipation questionnaire. *J Pediatr Psychol*. 2015;40:814-824.
4. van Ginkel R, Reitsma JB, Büller HA, et al. Childhood constipation: longitudinal follow-up beyond puberty. *Gastroenterology*. 2003;125:357-363.
5. Tabbers MM, Boluyt N, Berger MY, et al. Clinical practice: diagnosis and treatment of functional constipation. *Eur J Pediatr*. 2011;170:955-963.

6. Koppen IJN, Lammers LA, Benninga MA, et al. Management of functional constipation in children: therapy in practice. *Paediatr Drugs*. 2015;17:349-360.
7. Benninga MA, Buller HA, Heymans HS, et al. Is encopresis always the result of constipation? *Arch Dis Child*. 1994;71:186-193.
8. Koppen IJN, von Gontard A, Chase J, et al. Management of functional nonretentive fecal incontinence in children: recommendations from the International Children's Continence Society. *J Pediatr Urol*. 2016;12:56-64.
9. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011;62:381-396.
10. Milla PJ. Irritable bowel syndrome in childhood. *Gastroenterology*. 2001;120:287-290.
11. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology*. 2011;140:91-100.
12. Hubbard CS, Becerra L, Heinz N, et al. Abdominal pain, the adolescent and altered brain structure and function. *PLoS ONE*. 2016;11:e0156545.
13. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology*. 2000;118:842-848.
14. Kern MK, Shaker R. Cerebral cortical registration of subliminal visceral stimulation. *Gastroenterology*. 2002;122:290-298.
15. Liu X, Silverman A, Kern M, et al. Excessive coupling of the salience network with intrinsic neurocognitive brain networks during rectal distension in adolescents with irritable bowel syndrome: a preliminary report. *Neurogastroenterol Motil*. 2016;28:43-53.
16. Mayer EAA, Aziz Q, Coen S, et al. Brain imaging approaches to the study of functional GI disorders: a Rome working team report. *Neurogastroenterol Motil*. 2009;21:579-596.
17. Silverman DH, Munakata JA, Ennes H, et al. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology*. 1997;112:64-72.
18. Moisset X, Bouhassira D, Denis D, et al. Anatomical connections between brain areas activated during rectal distension in healthy volunteers: a visceral pain network. *Eur J Pain*. 2010;14:142-148.
19. Zhu Q, Cai W, Zheng J, et al. Distinct resting-state brain activity in patients with functional constipation. *Neurosci Lett*. 2016;632:141-146.
20. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut*. 1999;45(Suppl 2):II60-II68.
21. Elsenbruch S, Rosenberger C, Enck P, et al. Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study. *Gut*. 2010;59:489-495.
22. Coen SJ, Aziz Q, Yágüez L, et al. Effects of attention on visceral stimulus intensity encoding in the male human brain. *Gastroenterology*. 2008;135:2065-2074, 2074.e1.
23. Scholte EM, Ploeg JD. De ontwikkeling en toetsing van de ADHD-vragenlijst. *Kind en Adolesc*. 1999;20:50-60.
24. Muris P, Merckelbach H, Schmidt H, et al. The revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-R): Factor structure in normal children. *Pers Individ Dif*. 1998;26:99-112.
25. Ploeg van der HM. De, Zelf-Beoordelings Vragenlijst (STAI-DY). De ontwikkeling en validatie van een Nederlandstalige vragenlijst voor het meten van angst. *Tijdschr Psychiatr*. 1982;24:576-588.
26. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58:258-274.
27. Arhan P, Devroede G, Jehannin B, et al. Segmental colonic transit time. *Dis Colon Rectum*. 1981;24:625-629.
28. van den Berg MM, Voskuijl WP, Boeckxstaens GE, et al. Rectal compliance and rectal sensation in constipated adolescents, recovered adolescents and healthy volunteers. *Gut*. 2008;57:599-603.
29. Flandin G, Friston KJ. *Analysis of Family-Wise Error Rates in Statistical Parametric Mapping Using Random Field Theory*. 2016. https://arxiv.org/abs/1606.08199.
30. Voskuijl WP, Van Ginkel R, Benninga MA, et al. New insight into rectal function in pediatric defecation disorders: Disturbed rectal compliance is an essential mechanism in pediatric constipation. *J Pediatr*. 2006;148:62-67.
31. Camilleri M, Coulie B, Tack JF. Visceral hypersensitivity: facts, speculations, and challenges. *Gut*. 2001;48:125-131.
32. van den Berg MM, Bongers MEJ, Voskuijl WP, et al. No role for increased rectal compliance in pediatric functional constipation. *Gastroenterology*. 2009;137:1963-1969.
33. Wilder-Smith CH, Schindler D, Lovblad K, et al. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut*. 2004;53:1595-1601.
34. Aziz Q, Andersson JLL, Valind S, et al. Identification of human brain loci processing esophageal sensation using positron emission tomography. *Gastroenterology*. 1997;113:50-59.
35. Bernstein CN, Frankenstein UN, Rawsthorne P, et al. Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. *Am J Gastroenterol*. 2002;97:319-327.
36. van Oudenhove L, Vandenberghe J, Dupont P, et al. Cortical deactivations during gastric fundus distension in health: visceral pain-specific response or attenuation of "default mode" brain function? A H2 15O-PET study. *Neurogastroenterol Motil*. 2009;21:259-271.
37. Bonaz B, Baciu M, Papillon E, et al. Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study. *Am J Gastroenterol*. 2002;97:654-661.
38. McKiernan KA, Kaufman JN, Kucera-Thompson J, et al. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci*. 2003;15:394-408.
39. Kanazawa M, Hamaguchi T, Watanabe S, et al. Site-specific differences in central processing of visceral stimuli from the rectum and the descending colon in men. *Neurogastroenterol Motil*. 2010;22:173-180, e53.
40. Berman SM, Naliboff BD, Suyenobu B, et al. Sex differences in regional brain response to aversive pelvic visceral stimuli. *Am J Physiol Regul Integr Comp Physiol*. 2006;291:R268-R276.
41. Song GH, Venkatraman V, Ho KY, et al. Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls. *Pain*. 2006;126:79-90.
42. Kwan CL, Diamant NE, Pope G, et al. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. *Neurology*. 2005;65:1268-1277.
43. Devroede G, Girard G, Bouchoucha M, et al. Idiopathic constipation by colonic dysfunction. Relationship with personality and anxiety. *Dig Dis Sci*. 1989;34:1428-1433.
44. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1-38.
45. Binder JR. Task-induced deactivation and the "resting" state. *NeuroImage*. 2012;62:1086-1091.

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