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Review Article

The evolution of Magnetic Resonance Enterography in the assessment of motility disorders in children

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Highlights

- Gastrointestinal symptoms represent common clinical problems for paediatric populations.
- In adults, MRI to evaluate gastric physiology and motility is increasingly popular as a research tool.
- MRI's non-invasiveness, absence of ionising radiation and growing availability makes it a promising modality to help us better understand gastrointestinal symptoms in children.

Abstract:

Gastrointestinal symptoms including constipation, diarrhoea, pain and bloating represent some of the most common clinical problems for patients. These symptoms can often be managed with cheap, widely available medication or will spontaneously resolve. However, for many patients, chronic GI symptoms persist and frequently come to dominate their lives. At one end of the spectrum there is Inflammatory Bowel Disease (IBD) with a clearly defined but expensive treatment pathway. Contrasting with this is Irritable Bowel Syndrome (IBS), likely a collection of pathologies, has a poorly standardised pathway with unsatisfactory clinical outcomes. Managing GI symptoms in adult populations is a challenge. The clinical burden of gastrointestinal disease is also prevalent in paediatric populations and perhaps even harder to treat.

In this review we explore some of the recent advances in magnetic resonance imaging (MRI) to study the gastrointestinal tract. Complex in both its anatomical structure and its physiology we are likely missing key physiological markers of disease through relying on symptomatic descriptors of gut function. Using MRI we might be able to characterise previously opaque processes, such as non-propulsive contractility, that could lead to changes in how we understand even common symptoms like constipation. This review explores recent advances in the field in adult populations and examines how this safe, objective and increasingly available modality might be applied to paediatric populations.

Keywords: MRI
Dysmotility
Paediatric
Constipation

Introduction:

Gastrointestinal complaints including nausea, vomiting, abdominal pain and constipation represent some of the most common symptoms encountered by a physician[1], [2]. Where organic pathology has been excluded, gastrointestinal dysmotility is often implied as the underlying cause[3].

Aside from causing distress for the patient, GI symptoms can be tremendously frustrating for the clinician to treat and expensive for the healthcare provider to manage[4]. Patients will likely undergo batteries of tests to assess gastrointestinal function which all too often result in ambiguous findings that in many cases fail to inform medical management[5]–[7]. Pro-kinetics and other medications are effective in many patients but a significant proportion remain symptomatic and experience a reduced quality of life[8].

A challenge in adult populations, gastrointestinal dysmotility presents an even greater trial in paediatric clinics where risks of radiation exposure, medication side effects and a broader uncertainty of optimal treatment strategy (compounded by the varying onset of symptoms through development) complicate effective treatment for this population. Conditions including deranged gastric emptying, chronic intestinal pseudo-obstruction (CIPO), Hirschsprung disease and constipation represent, at best, a major impact to the quality of life and ability to thrive of the paediatric patient group[9].

The purpose of this review is to introduce the most recent advancements in medical imaging to assess gastrointestinal dysmotility. Optimal treatment of a patient comes from coupling an optimised diagnostic pathway with an efficacious treatment strategy. Diseases underpinned by gastrointestinal dysmotility are challenging because we do not have the tests to understand the nature of the underlying pathology. In adult populations, a number of recent studies have demonstrated new avenues to phenotype and drive fundamental understanding of gut function across a range of diseases (including dyspepsia, Crohn's and constipation) shared by paediatric populations.

Importantly, we have a range of medications that affect gut function. Without a means to direct them however, the 'trial and error ' method will continue to produce variable and occasionally unsatisfactory outcomes.

Dysmotility disorders in Children:

Several excellent reviews are currently available[4], [9], [10] summarising the main disorders of dysmotility in paediatric populations and the information summarised in these articles will not be repeated here. Instead, a brief overview of conditions affecting gastric, small bowel and colonic function is given, to provide context for the imaging advances component of this article. ***Delayed gastric emptying*** (referred to as gastroparesis by some, but not all, gastroenterologists) is characterised by delayed gastric emptying of solids or liquids in the absence of a mechanical obstruction[11], [12] . Up to 70% of cases are idiopathic, although secondary causes may include surgery, medication or infection[13], [14]. Diagnosis is currently made with scintigraphy and patients are managed with careful dietary planning and use of pro-kinetics however data is seemingly equivocal especially in adult populations where the majority of studies have taken place[12], [15], [16]. Complicating matters further, cardiac side-effects of drugs including domperidone[17], [18], and erythromycin[19], [20] have left many clinicians wary of using medications in paediatric cohorts[21].

Motor disorders of the small bowel include ***Chronic Intestinal Pseudo-Obstruction (CIPO)*** where loops of bowel may become distended in the absence of a mechanical obstruction[22]. The condition in adults is often secondary to diseases including scleroderma however idiopathic forms of the disease with a neuropathic or myopathic origin occur in a very small proportion of children[23], [24]. Although rare, management of these patients is challenging with malnutrition and complications of enteric feeding driving a high mortality rate in this population[25]. The use of pro-kinetics is limited[26] and radical interventions including intestinal transplants are currently used in some cases to address the most serious forms of CIPO[27].

Colonic dysmotility is complex and, like the stomach and small bowel, poorly understood despite a large body of research in adult populations. Two of the most commonly encountered disorders of dysmotility are Hirschsprung disease and constipation. ***Hirschsprung disease***, is life threatening with a relatively high prevalence of 1 in 10,000 births and a male predominance[28]. Hirschsprungs is believed to originate with mis-development of the enteric nervous system and takes several forms with varying effect on gut physiology[29]. Diagnostic tools include contrast enema, anorectal manometry and rectal biopsy (suction or open under anaesthesia). Surgery is required with the exception maybe of children diagnosed with short-segment Hirschsprung disease (internal anal sphincter achalasia)[4], [30]. ***Constipation*** contributes a reasonable proportion of the paediatric gastroenterology workload ranging from 1-30%[31] of patients but as high as 25% of Paediatric Gastroenterology Consultations[32]. Although rarely life threatening, constipation is distressing for patients and sufficiently common to make it difficult to deal with effectively in clinic.

MRI has been used in a number of recent studies to investigate conditions affecting stomach, small bowel and colon and has increasingly becoming a valuable research tool to investigate numerous aspects of gastrointestinal physiology. The above described gastroparesis, CIPO, Hirschsprung disease and constipation (especially in its chronic and medically recalcitrant form) represent key disorders of gastrointestinal motility in paediatric populations, which are well suited to exploration with MRI. We would like to stress however that the symptoms patients experience may be underpinned by a number of factors (e.g. psychological) and do not necessarily predicate motility. In the next section of this paper, we will discuss some of the key findings described over last five years in MR enterography and illustrate how this might be adapted to paediatric populations.

Use of MRI for assessment of gastrointestinal dysmotility

MRI for the stomach: Evaluation of gastric physiology with MRI is relatively well developed. Specifically for the investigation of transit and emptying[33], the technique is suitably validated and numerous studies have been conducted examining the impact of different meal types and compositions on emptying times. MRI itself has been compared with scintigraphy[34], [35] and good agreement has been observed. Beyond transit, MRI can offer functional information on contractility allowing a user to observe not only large propagating contractions but also, small sub-occlusive events that are difficult even to observe with existing techniques (e.g. manometry)[36]–[40].

The potential ability to combine multiple measurements of gastric physiology in one scanning session makes MRI versatile and informative modality[35], [37], [41]. In a feasibility study, MRI has recently been used in a combinatorial approach to investigate the interaction between emptying times and motility with a proposed surrogate for accommodation[41]. In a cohort of nine gastroparetic patients with controls, gastric emptying times were found to be decreased despite transit times being faster – a seemingly paradoxical situation. The surrogate measure for gastric accommodation (a potential confounder for the clinical picture) was derived through taking into account how the fundus expands following a meal. Although statistically insignificant, the data supported an altered ability of the fundus to expand in response to the meal providing a possible explanation for the accelerated transit in absence of increased motility. While this study of course requires repetition in a suitably powered investigation, exploring transit in the context of other potentially impactful and aberrant physiological processes is likely key for better understanding heterogeneous diseases such as dyspepsia. As repeated throughout this review, MRI is safe and a range of protocols in terms of different food stimuli might be developed making the test well poised for paediatric populations. From a practical perspective, many paediatric patients will undergo multiple gastric physiology tests (e.g. manometry , scintigraphy) and where the same data can be obtained from a single study a positive impact from patient experience and even hospital costs might be realised.

A broader discussion of the pros and cons of MRI is presented later in this article but specifically, the supine position in the scanner has been criticised as being non-physiological (although unproven in its effect)[42]. In practice, scintigraphy and manometry are performed (or at least inserted in the case of manometry) in the supine position. Upright, seated scanners are available offering an exciting future possibility for an MRI based workup and enable further validation or comparison against existing physiological techniques. Another persistent challenge with MRI data is its assessment and, while the quality of the images themselves have not changed much in recent years, the range of tools to assess gastric physiology have progressed. For meal volume segmentation, several articles have described semi-automated methods to facilitate transit scoring and motility assessment[43], [44].

MRI of the small bowel: Over the past decade, the use of MRI to assess Crohn's Disease has rapidly expanded with excellent soft tissue contrast for the assessment of structural changes in the bowel wall. Building on developments in cardiac MRI, the modality's ability to provide dynamic 'cine' data depicting motility has also seen increased use[45]. In practice, this motility imaging is used to provide greater confidence to the Radiologist when separating inflamed bowel (which is hypo-motile) from transiently collapsed loops which will often peristalses freely[46]–[49]. A situation that is less clear in anatomical images only.

The main advancement in the field has been the arrival of objective image processing techniques to assess small bowel motility[49]–[53]. Broadly, two approaches have been taken focusing on either segmental motility assessment exploring dysmotility at a specific lesion within the small bowel or, increasingly, global changes which may arise from low grade inflammation, neuro-muscular degeneration or in response to an external stimuli.

Segmental dysmotility in Crohn's disease has shown a strong negative relationship between the degree of inflammation and motility[46], [47]. Importantly, this relationship appears to be dynamic with a clinical improvement in the severity of the lesion correlating also with a return of motility in that bowel region[54]. A recent study demonstrated a 93.1 sensitivity and 76.5 specificity of motility to assess treatment response in CD demonstrating the clinical applicability of the technique.

Global motility assessment offers potentially important new insights into dysmotility and serves to summarise contractile activity across the bowel in a single, quantitative surrogate marker[55], [56]. In early studies, the approach was seen to be objective and repeatable in health volunteers scanned six weeks apart[55]. Provoking motility with neostigmine and suppressing it with Buscopan, each against a placebo control, produced strong significant results against known pharmacological influencers of motility. Moving into clinical studies, changes in global motility could be clearly seen in patients with Chronic Intestinal Pseudo-Obstruction who had a lower basal motility compared against healthy controls[57], [58]. Interestingly, in one study CIPO several subjects provoked with neostigmine had a robust increase in motility while other, with an underlying diagnosis of scleroderma, did not providing an interesting proof of concept study into the role MRI might have of phenotyping enteric disease[57]. Changes in global dysmotility have also been investigated in the context of patient symptoms with the ‘variation’ in motility correlating negatively against diarrhoea.

The prevalence of articles exploring small bowel dysmotility has been driven by the organ being so difficult to investigate in general. Ongoing work is now exploring the best ways to prepare the bowel. Traditionally, an oral hyper-osmotic drink (e.g. mannitol) has been used to distend the bowel and provide the good luminal contrast required by radiologists usually looking for evidence of IBD[59], [60]. The use of mannitol is non-physiological and several groups have begun exploring meal challenges which have a pronounced effect on motility in very short time scales. The ability to compare pre-post meal changes in motility represents an important advance and paradigm for MRI imaging where extended ambulatory studies are simply unfeasible.

One of the main challenges with exploring small bowel dysmotility is understanding normal ranges. This is difficult in adults currently and even more so in children where historically very little data exist. Nevertheless, for diseases such as CIPO the large calibre changes in bowel diameter together with depressed motility are easily identified with MRI and the technique represents an ideal approach for research and early clinical investigations in complex cases.

MRI of the colon: In contrast to the small bowel, the physiology of the large intestine has been relatively well studied with a range of techniques across numerous diseases[61], [62]. Transit time through the colon and manometry of the distal colon are routinely performed in many centres however the added value of these investigations is, in many cases, difficult to quantify in more complex disease[61]. MRI of the colon is relatively underdeveloped however there have been several advances in the last few years of note. First, dynamic imaging of the colon (as is used in the small bowel) can be used to reveal detailed physiological information depicting both small and large contractions propagating through the colon. Preparation with contrast (Moviprep) stimulates powerful contractile activity from baseline and, when imaged over long enough periods can be used to interrogate normal function[63]. In one recent study a combinatorial approach was used to assess motility in the context of fluid content and colonic volume to discriminate between chronic and functional constipation[64]. This paper postulated that disorganised contractility might underpin the latter and is corroborated by other studies with different techniques including wireless capsule endoscopy and manometry[65]–[68]. As with the small bowel and stomach, post processing has further enabled objective assessment of contractility with a key advance being respiration correction permitting the analysis of much longer time series (>10mins) without the patient needing to hold their breath (as is standard in many small bowel studies)[52], [63]. As colonic contractions are less frequent, the ability to scan for longer is a major advantage although protocols using a stimulus will likely be favoured for practical reasons in terms of scan times. An advantage of colonic scanning over small bowel is the ability to characterise contractile actions in a specific region of bowel; for example the entire ascending colon can be visualised in a single sagittal scan slice. Analysis of a specified portion of bowel enables spatio-temporal measurement of bowel wall motion that translate into real distances as opposed to the surrogate measures used in the small bowel[63]. This will enable better comparison to techniques like manometry, indeed this has already been performed[69], however the approaches are sufficiently different to prevent true validation.

Stressing the theme of multi-parametric assessment of gut function, MR-opaque capsules have been developed and used in several studies that enable simultaneous assessment of motility and transit time[70]. In 21 subjects, 20x7mm capsules filled with water and trace levels of gadolinium were ingested and showed clearly on T1 weighted MR imaging however agreement was relatively poor against a Lactose Ureide ^{13}C breath test, perhaps due to the large size. Smaller capsules may provide better agreement but in addition, the head of the meal can also be visualised with MRI providing two potential markers of transit alongside anatomical and motility imaging that make this an exciting area of development within the field.

Study of colonic physiology remains limited at present to just a few groups globally. However, there is potential value for paediatric conditions such as constipation and Hirschprung disease. To our knowledge, such diseases have yet to be scanned with MRI so we are collectively ignorant of exactly how functional imaging data of processes like motility might impact clinical decisions however, even as a research tool, it is likely that novel insights into such conditions might be achieved.

Pros and Cons of MRI:

A common challenge for conversations surrounding the use of MRI is the topic of cost. MRI remains one of the most in demand technologies in the modern hospital across specialities and its use for what is often considered to be ‘functional,’ untreatable conditions might be considered wasteful. However, in some diseases areas (specifically Crohn’s) MRI is now routinely used to monitor treatment suggesting an evolution in how the value of the technology is perceived. A common comparison is the expanding role of MRI in cardiology. Cardiology, despite having a numerous cost effective techniques (ECG, echos, CT etc) has benefited greatly from a surge of highly sophisticated advances in medical imaging making cardiac MR an essential part of many conditions’ work up[71]. We are not yet seeing the parallels clinically with MR enterography but the swell in research and development of a range of techniques favour a similar expansion in the role of MR within gastroenterology. In practice, MRI is likely less costly than alterative techniques especially those requiring radioisotopes or invasive and disposable componentry and as the number of MRI units increase and diagnostic value of the technique is better understood attitudes here will change.

Improvements in imaging analysis have certainly driven the use of MRI in research but the technique remains time consuming in practice both at the point of acquisition and analysis. Many established

GI physiology tests take place over a course of hours with repeat observations. This is simply not possible in a busy MRI unit and as such, novel protocols must be established. Some have been discussed above using simulant challenges to provoke a GI response and indeed, analogous approaches are routinely used in cardiac MRI and we therefore do not believe that this invalidates the approach rather demands a change in popular thinking. Additional considerations arise from patient tolerance to MRI scanning. Many adults struggle to comply with imaging protocols and his can be even more difficult in paediatric populations. Nevertheless, MRI scanning is very common across paediatric care and even for IBD. Although a failure rate is present steps can be taken with training, reassurance from friends, family and skilled radiographers to maximise compliance.

Beyond the potential described in the previous section, one of the key strengths of MRI is safety and non-invasiveness making it well suited to young and vulnerable paediatric populations. One of the greatest challenges for research in this field is a paucity of control and healthy data to which we might compare patient cases. Even if MRI does not become the premier method for assessing GI dysmotility the opportunity to collect healthy range data make it a really important test for more broadly informing the field and enabling advances going forward.

Conclusion

We live in an exciting time for the improvement in our understanding of gastrointestinal disease. Advances in biomedical imaging allow real-time visualisation and quantitation of the gut. The opportunity to gain novel insights into complex diseases and thereafter to apply our growing armamentarium of therapeutic strategies ought to be of tremendous interest to researchers and clinical practitioners in the field alike and we hope that this review offers some insights as to how the field might evolve.

Conflict of Interest statement

Alex Menys is the Founder and CEO of Motilent, a medical imaging technology company

Stuart Taylor performs contracting work for Robarts Clinical Trials

[1] J. S. Hyams, C. Di Lorenzo, M. Saps, R. J. Shulman, A. Staiano, and M. van Tilburg, "Childhood Functional Gastrointestinal Disorders: Child/Adolescent," *Gastroenterology*, vol. 150, no. 6, p. 1456–1468.e2, May 2016.

[2] M. A. Benninga, S. Nurko, C. Faure, P. E. Hyman, I. St. James Roberts, and N. L. Schechter, "Childhood Functional Gastrointestinal Disorders: Neonate/Toddler," *Gastroenterology*, vol. 150, no. 6, p. 1443–1455.e2, May 2016.

[3] S. Nurko, "Motility Disorders in Children," *Pediatr. Clin. North Am.*, vol. 64, no. 3, pp. 593–612, Jun. 2017.

[4] B. Chumpitazi and S. Nurko, "Pediatric gastrointestinal motility disorders: challenges and a clinical update.," *Gastroenterol. Hepatol. (N. Y).*, vol. 4, no. 2, pp. 140–8, Feb. 2008.

[5] P. L. Lu, M. Moore-Clingenpeel, D. Yacob, C. Di Lorenzo, and H. M. Mousa, "The rising cost of hospital care for children with gastroparesis: 2004-2013," *Neurogastroenterol. Motil.*, vol. 28, no. 11, pp. 1698–1704, Nov. 2016.

[6] R. Park, S. Mikami, J. LeClair, A. Bollom, C. Lembo, S. Sethi, A. Lembo, M. Jones, V. Cheng, E. Friedlander, and S. Nurko, "Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009," *Neurogastroenterol. Motil.*, vol. 27, no. 5, pp. 684–692, May 2015.

[7] A. Alioto, C. Di Lorenzo, M. L. Montgomery, and D. Yacob, "High Cost and Low Yield: The Diagnostic Evaluation of Rumination Syndrome in Pediatrics," *J. Pediatr.*, vol. 185, pp. 155–159, Jun. 2017.

[8] J. W. Varni, C. B. Bendo, R. J. Shulman, M. M. Self, S. Nurko, J. P. Franciosi, M. Saps, S. Saeed, G. M. Zacur, C. Vaughan Dark, J. F. Pohl, and for the P. Q. of L. I. G. S. M. T. S. Pediatric Quality of Life Inventory™ Gastrointestinal Symptoms Module Testing Study Consortium, "Interpretability of the PedsQL™ Gastrointestinal Symptoms Scales and Gastrointestinal Worry Scales in Pediatric Patients With Functional and Organic Gastrointestinal Diseases.," *J. Pediatr. Psychol.*, vol. 40, no. 6, pp. 591–601, Jul. 2015.

[9] L. Ambartsumyan and L. Rodriguez, "Gastrointestinal motility disorders in children.," *Gastroenterol. Hepatol. (N. Y).*, vol. 10, no. 1, pp. 16–26, Jan. 2014.

[10] A. Rasquin, C. Di Lorenzo, D. Forbes, E. Guiraldes, J. S. Hyams, A. Staiano, L. S. Walker, P. B. Sullivan, J. Tobin, N. Ryan, C. Di Lorenzo, and D. A. Brent, "Childhood Functional Gastrointestinal Disorders: Child/Adolescent," *Gastroenterology*, vol. 130, no. 5, pp. 1527–1537, Apr. 2006.

[11] S.-Y. Park, A. Acosta, M. Camilleri, D. Burton, W. S. Harmsen, J. Fox, and L. A. Szarka, "Gastric Motor Dysfunction in Patients With Functional Gastroduodenal Symptoms," *Am. J. Gastroenterol.*, vol. 112, no. 11, pp. 1689–1699, Nov. 2017.

[12] P. Janssen, M. Scott Harris, M. Jones, T. Masaoka, R. Farré, H. Törnblom, L. Van Oudenhove, M. Simrén, and J. Tack, "The Relation Between Symptom Improvement and Gastric Emptying in the Treatment of Diabetic and Idiopathic Gastroparesis," *Am. J. Gastroenterol.*, vol. 108, no. 9, pp. 1382–1391, Sep. 2013.

[13] L. Rodriguez, K. Irani, H. Jiang, and A. M. Goldstein, “Clinical Presentation, Response to Therapy, and Outcome of Gastroparesis in Children,” *J. Pediatr. Gastroenterol. Nutr.*, vol. 55, no. 2, pp. 185–190, Aug. 2012.

[14] S. Waseem, S. Islam, G. Kahn, B. Moshiree, and N. J. Talley, “Spectrum of Gastroparesis in Children,” *J. Pediatr. Gastroenterol. Nutr.*, vol. 55, no. 2, pp. 166–172, Aug. 2012.

[15] K. Maganti and K. Onyemere, “Oral erythromycin and symptomatic relief of gastroparesis: a systematic review,” *Am. J.*, 2003.

[16] A. Sturm, G. Holtmann, H. Goebell, and G. Gerken, “Prokinetics in patients with gastroparesis: a systematic analysis.,” *Digestion*, vol. 60, no. 5, pp. 422–7.

[17] B. Drolet, G. Rousseau, P. Daleau, R. Cardinal, and J. Turgeon, “Domperidone Should Not Be Considered a No-Risk Alternative to Cisapride in the Treatment of Gastrointestinal Motility Disorders,” *Circulation*, vol. 102, no. 16, 2000.

[18] C. van Noord, J. P. Dieleman, G. van Herpen, K. Verhamme, and M. C. J. M. Sturkenboom, “Domperidone and Ventricular Arrhythmia or Sudden Cardiac Death,” *Drug Saf.*, vol. 33, no. 11, pp. 1003–1014, Nov. 2010.

[19] P. Milberg, L. Eckardt, H.-J. Bruns, J. Biertz, S. Ramtin, N. Reinsch, D. Fleischer, P. Kirchhof, L. Fabritz, G. Breithardt, and W. Haverkamp, “Divergent Proarrhythmic Potential of Macrolide Antibiotics Despite Similar QT Prolongation: Fast Phase 3 Repolarization Prevents Early Afterdepolarizations and Torsade de Pointes,” *J. Pharmacol. Exp. Ther.*, vol. 303, no. 1, pp. 218–225, Oct. 2002.

[20] W. A. Ray, K. T. Murray, S. Meredith, S. S. Narasimhulu, K. Hall, and C. M. Stein, “Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes,” *N. Engl. J. Med.*, vol. 351, no. 11, pp. 1089–1096, Sep. 2004.

[21] E. M. Tillman, K. S. Smetana, L. Bantu, and M. G. Buckley, “Pharmacologic Treatment for Pediatric Gastroparesis: A Review of the Literature.,” *J. Pediatr. Pharmacol. Ther.*, vol. 21, no. 2, pp. 120–32, 2016.

[22] J. M. Fell, V. V Smith, and P. J. Milla, “Infantile chronic idiopathic intestinal pseudo-obstruction: the role of small intestinal manometry as a diagnostic tool and prognostic indicator.,” *Gut*, vol. 39, no. 2, pp. 306–11, Aug. 1996.

[23] J. E. Maldonado, J. A. Gregg, P. A. Green, and A. L. Brown, “Chronic idiopathic intestinal pseudo-obstruction.,” *Am. J. Med.*, vol. 49, no. 2, pp. 203–12, Aug. 1970.

[24] S. Butt and A. Emmanuel, “Systemic sclerosis and the gut.,” *Expert Rev. Gastroenterol. Hepatol.*, vol. 7, no. 4, pp. 331–9, May 2013.

[25] H. Mousa, P. E. Hyman, J. Cocjin, A. F. Flores, and C. Di Lorenzo, “Long-term outcome of congenital intestinal pseudoobstruction.,” *Dig. Dis. Sci.*, vol. 47, no. 10, pp. 2298–305, Oct. 2002.

[26] B. P. Raphael, S. Nurko, H. Jiang, K. Hart, D. S. Kamin, T. Jaksic, and C. Duggan, “Cisapride improves enteral tolerance in pediatric short-bowel syndrome with dysmotility.,” *J. Pediatr. Gastroenterol. Nutr.*, vol. 52, no. 5, pp. 590–4, May 2011.

[27] C. Loinaz, M. M. Rodríguez, T. Kato, N. Mittal, R. L. Romaguera, J. H. Bruce, S. Nishida, D. Levi, J. Madariaga, and A. G. Tzakis, “Intestinal and multivisceral transplantation in children with

severe gastrointestinal dysmotility," *J. Pediatr. Surg.*, vol. 40, no. 10, pp. 1598–1604, Oct. 2005.

[28] K. E. Best, M.-C. Addor, L. Arriola, E. Balku, I. Barisic, F. Bianchi, E. Calzolari, R. Curran, B. Doray, E. Draper, E. Garne, M. Gatt, M. Haeusler, J. Bergman, B. Khoshnood, K. Klungsoyr, C. Martos, A. Materna-Kiryluk, C. Matias Dias, B. McDonnell, C. Mullaney, V. Nelen, M. O'Mahony, A. Queisser-Luft, H. Randrianaivo, A. Rissmann, C. Rounding, A. Sipek, R. Thompson, D. Tucker, D. Wellesley, N. Zymak-Zakutnia, and J. Rankin, "Hirschsprung's disease prevalence in Europe: A register based study," *Birth Defects Res. Part A Clin. Mol. Teratol.*, vol. 100, no. 9, pp. 695–702, Sep. 2014.

[29] N. E. Butler Tjaden and P. A. Trainor, "The developmental etiology and pathogenesis of Hirschsprung disease," *Transl. Res.*, vol. 162, no. 1, pp. 1–15, Jul. 2013.

[30] S. Obata, S. Fukahori, M. Yagi, M. Suzuki, S. Ueno, K. Ushijima, and T. Taguchi, "Internal anal sphincter achalasia: data from a nationwide survey of allied disorders of Hirschsprung's disease in Japan," *Surg. Today*, vol. 47, no. 12, pp. 1429–1433, Dec. 2017.

[31] M. M. van den Berg, M. A. Benninga, and C. Di Lorenzo, "Epidemiology of Childhood Constipation: A Systematic Review," *Am. J. Gastroenterol.*, vol. 101, no. 10, pp. 2401–2409, Oct. 2006.

[32] O. Liem, J. Harman, M. Benninga, K. Kelleher, H. Mousa, and C. Di Lorenzo, "Health Utilization and Cost Impact of Childhood Constipation in the United States," *J. Pediatr.*, vol. 154, no. 2, pp. 258–262, Feb. 2009.

[33] C. Feinle, P. Kunz, P. Boesiger, M. Fried, and W. Schwizer, "Scintigraphic validation of a magnetic resonance imaging method to study gastric emptying of a solid meal in humans.," *Gut*, vol. 44, no. 1, pp. 106–11, Jan. 1999.

[34] C. Feinle, P. Kunz, P. Boesiger, M. Fried, and W. Schwizer, "Scintigraphic validation of a magnetic resonance imaging method to study gastric emptying of a solid meal in humans," *Gut*, vol. 44, no. 1, pp. 106–111, Jan. 1999.

[35] N. Hayakawa, Y. Nakamoto, T. F. Chen-Yoshikawa, A. Kido, T. Ishimori, K. Fujimoto, T. Yamada, M. Sato, A. Aoyama, H. Date, and K. Togashi, "Gastric motility and emptying assessment by magnetic resonance imaging after lung transplantation: correlation with gastric emptying scintigraphy," *Abdom. Radiol.*, vol. 42, no. 3, pp. 818–824, Mar. 2017.

[36] l. kloetzer, w. d. chey, r. w. mccallum, k. l. koch, j. m. wo, m. sitrin, l. a. katz, j. m. lackner, h. p. parkman, g. e. wilding, j. r. semler, w. l. hasler, and b. kuo, "Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule," *Neurogastroenterol. Motil.*, vol. 22, no. 5, pp. 527–33, e117, Jan. 2010.

[37] H. Teramoto, T. Shimizu, H. Yogo, Y. Nishimiya, S. Hori, T. Kosugi, and S. Nakayama, "Assessment of gastric emptying and duodenal motility upon ingestion of a liquid meal using rapid magnetic resonance imaging," *Exp. Physiol.*, vol. 97, no. 4, pp. 516–524, Apr. 2012.

[38] L. A. Szarka and M. Camilleri, "Methods for measurement of gastric motility," *AJP Gastrointest. Liver Physiol.*, vol. 296, no. 3, pp. G461–G475, Jan. 2009.

[39] I. M. de Zwart, B. Mearadji, H. J. Lamb, P. H. C. Eilers, A. A. M. Masclee, A. de Roos, and P. Kunz, "Gastric motility: comparison of assessment with real-time MR imaging or barostat measurement initial experience.," *Radiology*, vol. 224, no. 2, pp. 592–7, Aug. 2002.

[40] W. Ajaj, S. C. Goehde, N. Papanikolaou, G. Holtmann, S. G. Ruehm, J. F. Debatin, and T. C. Lauenstein, “Real time high resolution magnetic resonance imaging for the assessment of gastric motility disorders.,” *Gut*, vol. 53, no. 9, pp. 1256–61, Sep. 2004.

[41] A. Menys, D. Keszthelyi, H. Fitzke, A. Fikree, D. Atkinson, Q. Aziz, and S. A. Taylor, “A magnetic resonance imaging study of gastric motor function in patients with dyspepsia associated with Ehlers-Danlos Syndrome-Hypermobility Type: A feasibility study,” *Neurogastroenterol. Motil.*, vol. 29, no. 9, p. e13090, Sep. 2017.

[42] H. Fruehauf, A. Steingoetter, M. R. Fox, M. A. Kwiatek, P. Boesiger, W. Schwizer, M. Fried, M. Thumshirn, and O. Goetze, “Characterization of gastric volume responses and liquid emptying in functional dyspepsia and health by MRI or barostat and simultaneous C-acetate breath test.,” *Neurogastroenterol. Motil.*, vol. 21, no. 7, pp. 697-e37, Jul. 2009.

[43] M. A. Kwiatek, A. Steingoetter, A. Pal, D. Menne, J. G. Brasseur, G. S. Hebbard, P. Boesiger, M. Thumshirn, M. Fried, and W. Schwizer, “Quantification of distal antral contractile motility in healthy human stomach with magnetic resonance imaging,” *J. Magn. Reson. Imaging*, vol. 24, no. 5, pp. 1101–1109, Nov. 2006.

[44] S. Bickelhaupt, J. M. Froehlich, R. Cattin, S. Raible, H. Bouquet, U. Bill, and M. A. Patak, “Software-supported evaluation of gastric motility in MRI: A feasibility study,” *J. Med. Imaging Radiat. Oncol.*, vol. 58, no. 1, pp. 11–17, Feb. 2014.

[45] J. Panes, Y. Bouhnik, W. Reinisch, J. Stoker, S. A. Taylor, D. C. Baumgart, S. Danese, S. Halligan, B. Marincek, C. Matos, L. Peyrin-Biroulet, J. Rimola, G. Rogler, G. van Assche, S. Ardizzone, A. Ba-Ssalamah, M. A. Bali, D. Bellini, L. Biancone, F. Castiglione, R. Ehehalt, R. Grassi, T. Kucharzik, F. Maccioni, G. Maconi, F. Magro, J. Martín-Comín, G. Morana, D. Pendsé, S. Sebastian, A. Signore, D. Tolan, J. A. Tielbeek, D. Weishaupt, B. Wiarda, and A. Laghi, “Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines.,” *J. Crohns. Colitis*, vol. 7, no. 7, pp. 556–85, Aug. 2013.

[46] A. Menys, D. Atkinson, F. Odille, A. Ahmed, M. Novelli, M. Rodriguez-Justo, I. Proctor, S. Punwani, S. Halligan, and S. A. Taylor, “Quantified terminal ileal motility during MR enterography as a potential biomarker of Crohn’s disease activity: a preliminary study.,” *Eur. Radiol.*, vol. 22, no. 11, pp. 2494–501, Nov. 2012.

[47] J. L. Cullmann, S. Bickelhaupt, J. M. Froehlich, Z. Szucs-Farkas, R. Tutuian, N. Patuto, H. Dawson, and M. A. Patak, “MR imaging in Crohn’s disease: correlation of MR motility measurement with histopathology in the terminal ileum.,” *Neurogastroenterol. Motil.*, vol. 25, no. 9, pp. 749-e577, Sep. 2013.

[48] S. Bickelhaupt, J. M. Froehlich, R. Cattin, N. Patuto, R. Tutuian, K. U. Wentz, J. L. Culmann, S. Raible, H. Bouquet, U. Bill, and M. A. Patak, “Differentiation between active and chronic Crohn’s disease using MRI small-bowel motility examinations — Initial experience,” *Clin. Radiol.*, vol. 68, no. 12, pp. 1247–1253, 2013.

[49] M. L. Hahnemann, F. Nensa, S. Kinner, G. Gerken, and T. C. Lauenstein, “Motility mapping as evaluation tool for bowel motility: Initial results on the development of an automated color-coding algorithm in cine MRI.,” *J. Magn. Reson. Imaging*, Jan. 2014.

[50] F. Odille, A. Menys, A. Ahmed, S. Punwani, S. A. Taylor, and D. Atkinson, “Quantitative assessment of small bowel motility by nonrigid registration of dynamic MR images.,” *Magn. Reson. Med.*, vol. 68, no. 3, pp. 783–93, Sep. 2012.

[51] S. Bickelhaupt, J. M. Froehlich, R. Cattin, S. Raible, H. Bouquet, U. Bill, and M. A. Patak, "Software-assisted small bowel motility analysis using free-breathing MRI: Feasibility study.," *J. Magn. Reson. Imaging*, vol. 39, no. 1, pp. 17–23, Jan. 2014.

[52] A. Menys, V. Hamy, J. Makanyanga, C. Hoad, P. Gowland, F. Odille, S. A. Taylor, and D. Atkinson, "Dual registration of abdominal motion for motility assessment in free-breathing data sets acquired using dynamic MRI.," *Phys. Med. Biol.*, vol. 59, no. 16, pp. 4603–19, Aug. 2014.

[53] A. M. J. Sprengers, M. P. Van Der Paardt, F. M. Zijta, M. W. A. Caan, R. M. Lamerichs, A. J. Nederveen, and J. Stoker, "Use of continuously MR tagged imaging for automated motion assessment in the abdomen: A feasibility study.," *J. Magn. Reson. Imaging*, vol. 36, no. 2, pp. 492–7, 2012.

[54] A. A. Plumb, A. Menys, E. Russo, D. Prezzi, G. Bhatnagar, R. Vega, S. Halligan, T. R. Orchard, and S. A. Taylor, "Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease.," *Aliment. Pharmacol. Ther.*, Jun. 2015.

[55] A. Menys, S. A. Taylor, A. Emmanuel, A. Ahmed, A. A. Plumb, F. Odille, A. Alam, S. Halligan, and D. Atkinson, "Global Small Bowel Motility: Assessment with Dynamic MR Imaging," vol. 269, no. 2, pp. 443–450, Nov. 2013.

[56] M. P. van der Paardt, A. M. J. Sprengers, F. M. Zijta, R. Lamerichs, A. J. Nederveen, and J. Stoker, "Noninvasive automated motion assessment of intestinal motility by continuously tagged MR imaging.," *J. Magn. Reson. Imaging*, vol. 39, no. 1, pp. 9–16, Jan. 2014.

[57] A. Menys, S. Butt, A. Emmanuel, A. A. Plumb, A. Fikree, C. Knowles, D. Atkinson, N. Zarate, S. Halligan, and S. A. Taylor, "Comparative quantitative assessment of global small bowel motility using magnetic resonance imaging in chronic intestinal pseudo-obstruction and healthy controls," *Neurogastroenterol. Motil.*, vol. 28, no. 3, pp. 376–383, Mar. 2016.

[58] H. Ohkubo, T. Kessoku, A. Fuyuki, H. Iida, M. Inamori, T. Fujii, H. Kawamura, Y. Hata, N. Manabe, T. Chiba, T. C. Kwee, K. Haruma, N. Matsuhashi, A. Nakajima, and T. Takahara, "Assessment of small bowel motility in patients with chronic intestinal pseudo-obstruction using cine-MRI.," *Am. J. Gastroenterol.*, vol. 108, no. 7, pp. 1130–9, Jul. 2013.

[59] T. C. Lauenstein, H. Schneemann, F. M. Vogt, C. U. Herborn, S. G. Ruhm, and J. F. Debatin, "Optimization of oral contrast agents for MR imaging of the small bowel.," *Radiology*, vol. 228, no. 1, pp. 279–83, Jul. 2003.

[60] K. Schunk, A. Kern, K. Oberholzer, P. Kalden, I. Mayer, T. Orth, and R. Wanitschke, "Hydro-MRI in Crohn's disease: appraisal of disease activity.," *Invest. Radiol.*, vol. 35, no. 7, pp. 431–7, Jul. 2000.

[61] L. A. Szarka and M. Camilleri, "Methods for the assessment of small-bowel and colonic transit.," *Semin. Nucl. Med.*, vol. 42, no. 2, pp. 113–23, Mar. 2012.

[62] M. Camilleri and D. R. Linden, "Measurement of Gastrointestinal and Colonic Motor Functions in Humans and Animals," *Cell. Mol. Gastroenterol. Hepatol.*, vol. 2, no. 4, pp. 412–428, Jul. 2016.

[63] C. L. Hoad, A. Menys, K. Garsed, L. Marciani, V. Hamy, K. Murray, C. Costigan, D. Atkinson, G. Major, R. C. Spiller, S. A. Taylor, and P. A. Gowland, "Colon wall motility: comparison of novel quantitative semi-automatic measurements using cine MRI.," *Neurogastroenterol. Motil.*,

Nov. 2015.

[64] C. Lam, G. Chaddock, L. Marciani, C. Costigan, J. Paul, E. Cox, C. Hoad, A. Menys, S. Pritchard, K. Garsed, S. Taylor, D. Atkinson, P. Gowland, and R. Spiller, “Colonic response to laxative ingestion as assessed by MRI differs in constipated irritable bowel syndrome compared to functional constipation.,” *Neurogastroenterol. Motil.*, vol. 28, no. 6, pp. 861–70, Jun. 2016.

[65] K. Ravi, A. E. Bharucha, M. Camilleri, D. Rhoten, T. Bakken, and A. R. Zinsmeister, “Phenotypic variation of colonic motor functions in chronic constipation.,” *Gastroenterology*, vol. 138, no. 1, pp. 89–97, Jan. 2010.

[66] W. L. Hasler, R. J. Saad, S. S. Rao, G. E. Wilding, H. P. Parkman, K. L. Koch, R. W. McCallum, B. Kuo, I. Sarosiek, M. D. Sitrin, J. R. Semler, and W. D. Chey, “Heightened colon motor activity measured by a wireless capsule in patients with constipation: relation to colon transit and IBS.,” *Am. J. Physiol. Gastrointest. Liver Physiol.*, vol. 297, no. 6, pp. G1107-14, Dec. 2009.

[67] L. Wiklendt, S. D. Mohammed, S. M. Scott, and P. G. Dinning, “Classification of normal and abnormal colonic motility based on cross-correlations of pancolonic manometry data.,” *Neurogastroenterol. Motil.*, vol. 25, no. 3, pp. e215-23, Mar. 2013.

[68] P. G. Dinning, L. Wiklendt, L. Maslen, V. Patton, H. Lewis, J. W. Arkwright, D. A. Wattchow, D. Z. Lubowski, M. Costa, and P. A. Bampton, “Colonic motor abnormalities in slow transit constipation defined by high resolution, fibre-optic manometry.,” *Neurogastroenterol. Motil.*, vol. 27, no. 3, pp. 379–88, Mar. 2015.

[69] S. Kirchhoff, M. Nicolaus, J. Schirra, M. F. Reiser, B. Göke, and A. Lienemann, “Assessment of colon motility using simultaneous manometric and functional cine-MRI analysis: preliminary results.,” *Abdom. Imaging*, vol. 36, no. 1, pp. 24–30, Feb. 2011.

[70] G. Chaddock, C. Lam, C. L. Hoad, C. Costigan, E. F. Cox, E. Placidi, I. Thexton, J. Wright, P. E. Blackshaw, A. C. Perkins, L. Marciani, P. A. Gowland, and R. C. Spiller, “Novel MRI tests of orocecal transit time and whole gut transit time: studies in normal subjects.,” *Neurogastroenterol. Motil.*, vol. 26, no. 2, pp. 205–14, Feb. 2014.

[71] G. Captur, C. Manisty, and J. C. Moon, “Cardiac MRI evaluation of myocardial disease,” *Heart*, vol. 102, no. 18, pp. 1429–1435, Sep. 2016.

Figure legend

Figure 1. A simple method for evaluating gastric motility by plotting the length of a line crossing the gastric lumen across several time points (images A,B & C). Computer algorithms can be used to perform this automatically which makes the process less time intensive. The length of the line at different time points can be plotted (dotted red line = actual data, solid red line = fitted) against time and a contraction determined by diameter change beneath a threshold (black dotted line) (D).

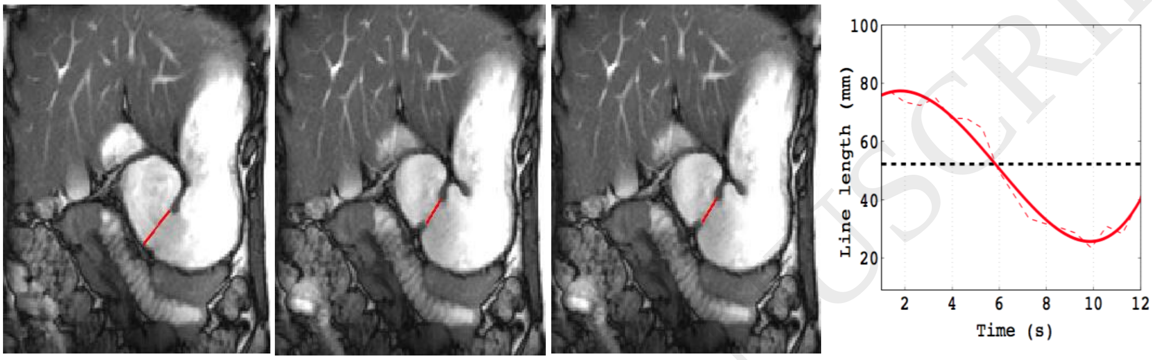

Figure 2. A) A single image from a dynamic 'cine' series of usually 20 images. B) the deformation fields generated by the image registration map how much each pixel image moves between the frames in the series. C) The summary of the deformation fields as a motility map with areas of high movement in red and low in blue. Red arrows indicate region of inflamed bowel and lower motility index.