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ORIGINAL ARTICLE

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The MRI colonic function test: Reproducibility of the Macrogol stimulus challenge

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Abstract

Background: Magnetic resonance imaging (MRI) of the colonic response to a macrogol challenge drink can be used to assess the mechanisms underlying severe constipation. We measured the intrasubject reproducibility of MRI measures of colonic function to aid their implementation as a possible clinical test.

Methods: Healthy participants attended for MRI on two occasions (identical protocols, minimum 1 week apart). They underwent a fasted scan and then consumed the macrogol drink. Subjects were scanned at 60 and 120 minutes, with maximum value reached used for comparison. The colonic volume, water content, mixing of colonic content and the movement of the colon walls were measured. Coefficients of variation and intraclass correlation coefficients (ICC) were calculated.

Results: Twelve participants completed the study: nine female, mean age 26 years (SD 5) and body mass index 24.8 kg/m^2 (SD 3.2). All measures consistently increased above baseline following provocation with macrogol. The volume, water content and content mixing had good intrasubject reproducibility (ICC volume = 0.84, water content = 0.93, mixing = 0.79, $P < .001$). With the wall movement, the response to the challenge was generally large, but more variable between visits resulting in a lower ICC overall (ascending colon = 0.65, descending colon = 0.76, $P < .001$).

Conclusions: The colonic response to the macrogol stimulus as assessed by MRI is heterogeneous but large compared to baseline, with moderate to good reproducibility, making the test suitable to study potential pathologies underlying GI disorders such as constipation. More data are needed to better define the normal range for comparison with patient groups who may have both hypo- and hypermotile responses.

KEYWORDS

colon, constipation, magnetic resonance imaging, reproducibility

Abbreviations: AC, ascending colon; bTFE, balanced turbo field echo; DC, descending colon; FC, functional constipation; GI, gastrointestinal; IBS-C, irritable bowel syndrome, constipation predominant; ICC, intraclass correlation coefficient; MRI, magnetic resonance imaging; RARE, rapid acquisition with relaxation enhancement; STMM, spatio-temporal motility technique; T120, time point 120 minutes after starting the macrogol drink; T60, time point 60 minutes after starting the macrogol drink; TBM, time to bowel movement.

1 | INTRODUCTION

Constipation is a common condition, affecting on average 14% of the world population.[1] For those affected, it can have a serious impact on quality of life[2] and associated economic cost.[3]

The latest Rome Criteria (Rome IV) split primary constipation into functional constipation (FC) and irritable bowel syndrome with constipation (IBS-C), distinguished by the presence or absence of pain in association with bowel habit. These conditions may have different underlying mechanisms, requiring quite different treatments. Distinguishing these conditions in the clinic based mostly on patient report leads to trial and error treatments which may explain why nearly 50% of patients are dissatisfied with their treatment.[4]

A novel diagnostic test using magnetic resonance imaging (MRI) based on the consumption of a macrogol challenge drink has been developed to define the underlying mechanisms of severe constipation.[5,6] This looked at assessment of the colonic volumes, water content and mixing of colonic chyme, as well as movements of the colon walls, critical components in defining organ function. This showed that there may be distinct differences between the two groups of patients, and if this is the case, then they would likely need different treatments.

It is currently unknown how reproducible the response of the colon is to this stimulus test. Previous studies have looked at the variability and reproducibility of other GI measurements such as gastric emptying and transit, as well as manometry techniques and have found considerable inter- and intrasubject variability using a variety of analytical methods including coefficients of variation, intraclass correlation coefficients (ICC) and Bland-Altman analysis.[7-11]

The main aim of this study was to measure the intrasubject reproducibility of these MRI colon function measures using an open-label study design in a group of healthy volunteers. A secondary aim was to assess the feasibility of measuring the motor function of the descending colon (not studied in previous work) since abnormalities of distal colon function are also likely to be an important determinants of bowel function.

Key Points

- A novel diagnostic test using MRI and a macrogol challenge drink can objectively assess colonic physiology (volume, fluid flow, wall motility, and water content). However, the reproducibility of these responses has not been investigated.
- This study assessed the intrasubject reproducibility of these colonic responses in healthy volunteers using identical study protocols on two separate occasions.
- Colonic water content, volumes, fluid flow, and motility all consistently increased above baseline values post stimulus. The colonic water, volume, and flow data had good intrasubject reproducibility. AC and DC motility were reasonably repeatable at baseline but the response to the challenge was variable between visits resulting in a lower ICC. This makes it a suitable test to study potential pathologies underlying GI disorders such as constipation.

2 | METHODS

2.1 | Study design

This was an open-label study examining the reproducibility of the response of the large intestine to acute ingestion of 500 to 1000 mL of

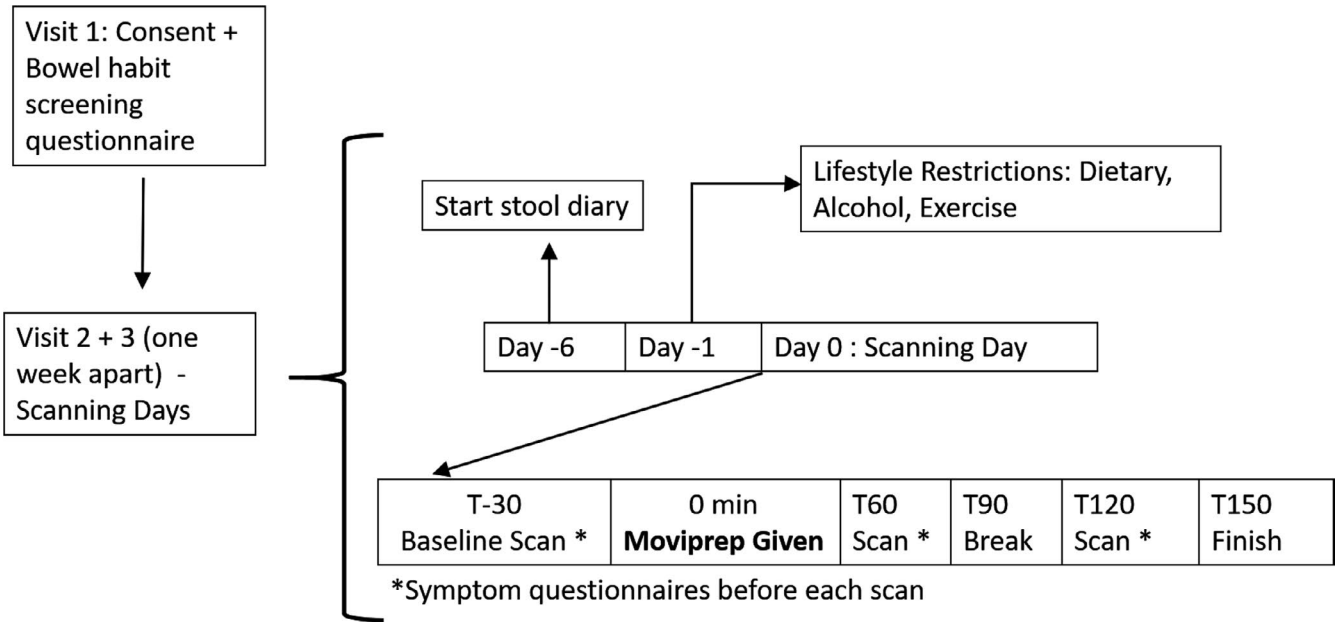

FIGURE 1 Schematic of the study day

poly-ethylene glycol and electrolyte solution (Moviprep®, Norgine Pharmaceuticals Ltd).

The study was approved by the Ethics Committee of the University of Nottingham (Nottingham, UK) [UoN FMHS D10052016 SPMIC MR]. The study was carried out according to Good Clinical Practice principles, and all participants gave written informed consent.

2.2 | Subjects

Twelve healthy volunteers were recruited from the general campus population at the University of Nottingham by advertisement. The inclusion criteria were male or female, 18-55 years of age and body mass index between 18 and 30 kg/m^2. The exclusion criteria were pregnancy, any history of serious acute or chronic illness especially gastrointestinal, use of medication known to affect gastrointestinal transit, such as opiates and constipating drugs, substance abuse and unsuitability for MRI scanning (such as pacemaker). Prior to each study visit, participants were asked to complete the Talley bowel habit questionnaire[12] and screening diary to ensure they did not suffer from recurrent abdominal pain and bowel frequency was normal (defined as bowel movements >2 and <10 over the 3 days prior to each MRI study day).

2.3 | Study day protocol

Each participant attended the study centre on two occasions, at least 1 week apart. They were asked to avoid strenuous exercise, dietary supplements and alcohol for 24 hours prior to the study visit and caffeine for 18 hours. On the morning of the scan, participants arrived fasted (from 10.30 PM the night before) at the study centre.

After completing the daily eligibility questionnaire, participants underwent a 20 - 30 minute MRI baseline scanning session. Participants then drank 10 mL/kg of body weight (rounded to 100 mL) of Moviprep®, at a rate of 2.5 mL/kg per 15 minutes. This was based on previous experience that using fixed doses of 1000 or 2000 mL made smaller subjects unduly nauseated so that they could not reliably consume the prescribed amounts introducing an uncontrolled source of variation between subjects. Participants underwent two further 20 - 30 minute scan sessions at 60 (T60) and 120 (T120) minutes after starting the macrogol drink (see schematic Figure 1).

Participants were asked to rate their symptoms of pain, bloating and flatulence as absent = 0, mild = 1, moderate = 2 and severe = 3 using the questionnaire of Tornblom[13] at baseline, immediately after finishing the drink (T60) and 60 minutes later (T120, Figure 1). Participants were also asked to record the time of their first bowel movement following the drink (TBM).

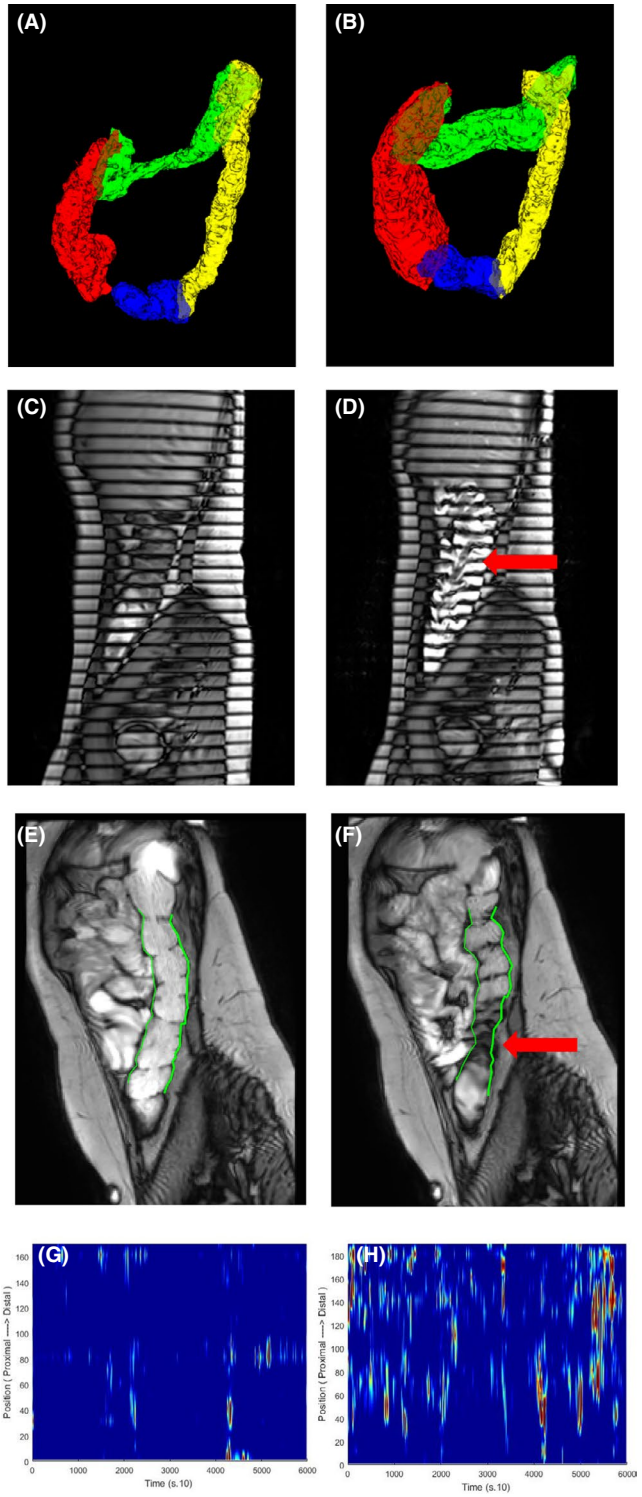

FIGURE 2 A + B, Pre- and post-stimulus anatomical 3D rendered images for analysis of colonic volume. C + D, Pre- and post-stimulus tagging images (content mixing) of the AC, in Figure C the tagging lines remain horizontal, whereas in D, they are distorted by fluid flow in the AC (arrow). E + F, Images from wall movement analysis, vertical lines are drawn at the edge of the descending colon which move with contractions (arrow). G + H, Pre- and post-stimulus STMM Maps produced from wall movement analysis, showing meal response

2.4 | MRI protocol

Imaging was carried out on a 3.0T Ingenia wide-bore scanner (Philips, Best, The Netherlands) with a parallel imaging SENSE abdominal body receiver coil. A range of MRI sequences were used to image the abdomen including:

1. Colonic regional and total volumes: a 3D coronal dual-echo fast field echo sequence with mDIXON reconstruction.[14]
2. Bowel Water Content: A single shot, coronal fast spin echo sequence (rapid acquisition with relaxation enhancement, RARE).
3. MRI content mixing measurement: A single 10 mm slice cine bTFE with tag lines 12 mm apart.
4. MRI wall movement measurement: Cine bTFE (balanced turbo field echo).

Full sequence information is detailed in Table S4. Data were acquired on an expiration breath-hold with duration between 18 and 24 seconds depending on the sequence (for the first three sequences) and monitored using a respiratory belt. The colon wall measurement sequence was duration 10 minutes with a temporal resolution of 1 s acquired during gentle free breathing.

TABLE 1 Summary data of all MRI endpoints measured

				CoV	CoV	Intraclass correlation coefficient (ICC)			
				(Intrasubject)	(Intersubject)	(Baseline and Maximum, Visit 1 vs Visit 2)			
Measurement	Time point	Visit 1	Visit 2	%	%		Lower	Upper	
Colon volume (mL)†	Baseline	728 ± 267	768 ± 246	14	34	0.84	0.67	0.93	<0.001
	Maximum	1226 ± 336	1199 ± 242	11	24				
	(Base-max)[a]	$P < .0001$	$P < .0001$						
Total water content (mL)†	Baseline	113 ± 63.3	108 ± 49	34	51	0.93	0.84	0.97	<0.001
	Maximum	1071 ± 266	1060 ± 313	18	27				
	(Base-max)[a]	$P < .0001$	$P < .0001$						
Colonic water content (mL)	Baseline	0 (0)	0 (0)	*	*	0.85	0.7	0.93	<0.001
	Maximum	538 ± 278	540 ± 242	29	48				
	(Base-Max)[b]	$P = .0005$	$P = .0005$						
Content mixing AC (%)	Baseline	18 ± 8	16 ± 6	14	41	0.76	0.49	0.89	<0.001
	Maximum	35 ± 10	30 ± 7	13	27				
	(Base-max)[a]	$P < .0001$	$P < .0001$						
Content mixing DC (%)	Baseline	23 ± 8	22 ± 7	15	33	0.62	0.3	0.81	<0.001
	Maximum	31 ± 11	28 ± 7	16	29				
	(Base-max)[a]	$P = .0106$	$P = .0177$						
Wall movement AC (a.u)	Baseline	272 (37-710)	135 (37-264)	85	94	0.65	0.35	0.83	<0.001
	Maximum	1886 (955-3669)	1877 (1613-2163)	32	70				
	(Base-Max)[b]	$P = .0015$	$P = .0005$						
Wall movement DC (a.u)	Baseline	258 (104-460)	441 (167-911)	64	76	0.76	0.53	0.89	<0.001
	Maximum	2249 (1786-2834)	1941 (1454-3864)	32	53				
	(Base-Max)[b]	$P = .0005$	$P = .0005$						
Time to Bowel Movement (min)		95 (95-113)	90 (51-133)	110	19	0.98	0.94	0.99	<0.001

Note: Data presented as either mean ± SD or median (interquartile range). All individual time point post-stimulus data in Table S3.

Abbreviations: AC, ascending colon; DC, descending colon.

[a]Paired *t* test.

[b]Paired Wilcoxon.

*CoV unable to be calculated due to the large number of zero data.

†Further segmented data in Tables S1 and S2.

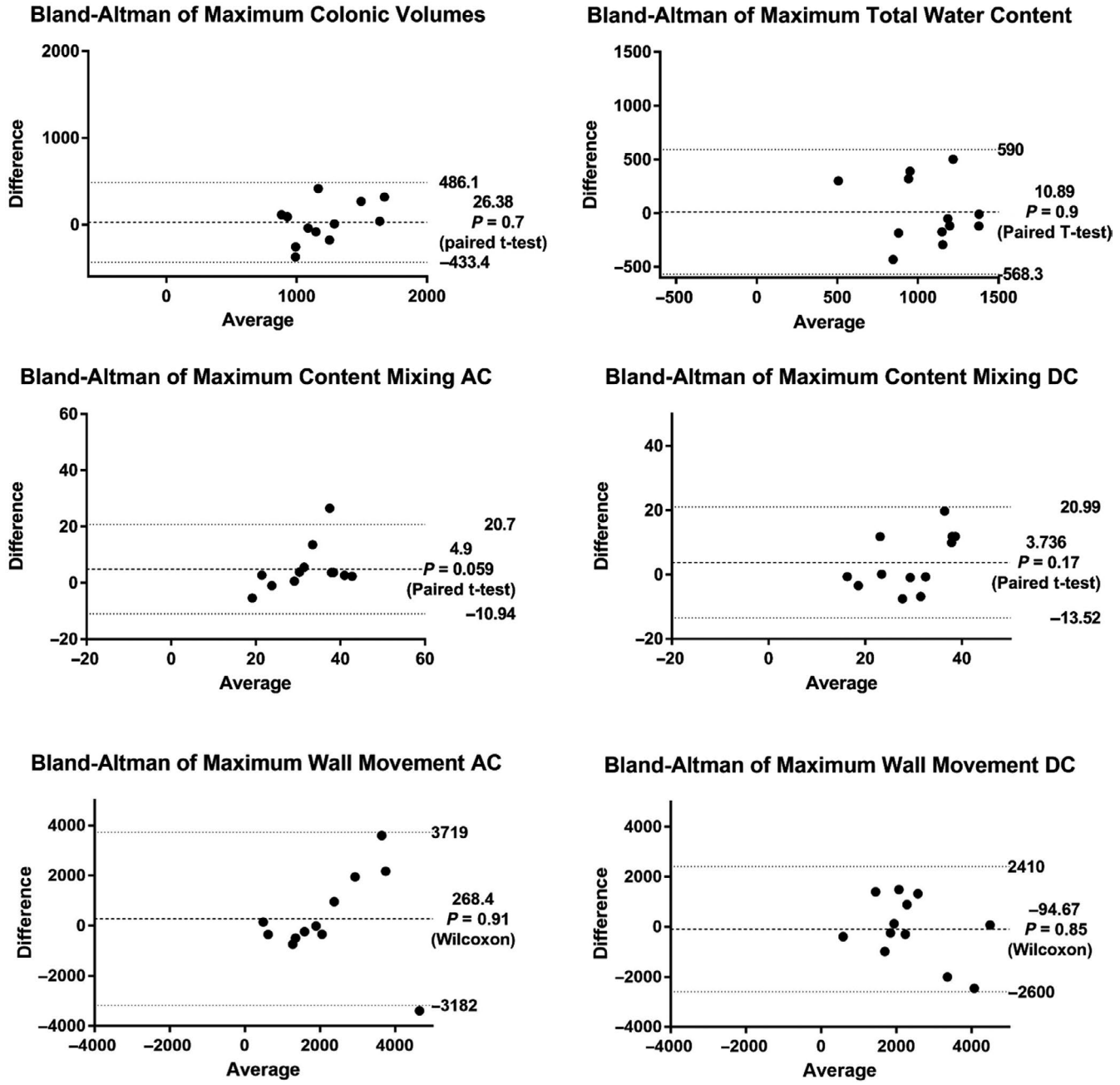

FIGURE 3 Bland-Altman plots showing difference vs average with dotted lines representing bias and 95% limits of agreement, and a paired *t* test or Wilcoxon test (if non-normal data) used to assess for significance of this bias

2.5 | Image analysis

Analyses were performed with automated and semi-automated image analysis software, Analyze9® (Mayo Clinic) and software written using Matlab® (The MathWorks Inc) and IDL® (Research Systems Inc). Colonic volumes and water content (mL) were measured as previously described.[15-17] For the colonic volume data, the slice thickness was increased to 5.4 mm by averaging three consecutive slices to reduce the number of images to be used in the analysis from 111 to 37. Colonic content mixing within the colon was assessed using the average coefficient of variance (%) for the colonic region of interest in the tagged cine MRI data.[17] This was calculated from mean and standard deviation maps of the voxel intensities measured across the time series cine data, with a user-defined region of interest drawn round the colon contents on the mean intensity map.

For the colonic wall movements, the untagged cine data were non-linearly registered across the time course using GIQuant® (Motilient Ltd).[18] The spatio-temporal motility technique (STMM) was then used to assess changes in luminal diameter with time (due to contractions) along the AC and DC using software written in Matlab,[19,20] and these data were used to calculate the combined velocity distance motility index (a.u.).[20] Briefly, the speed of the wall

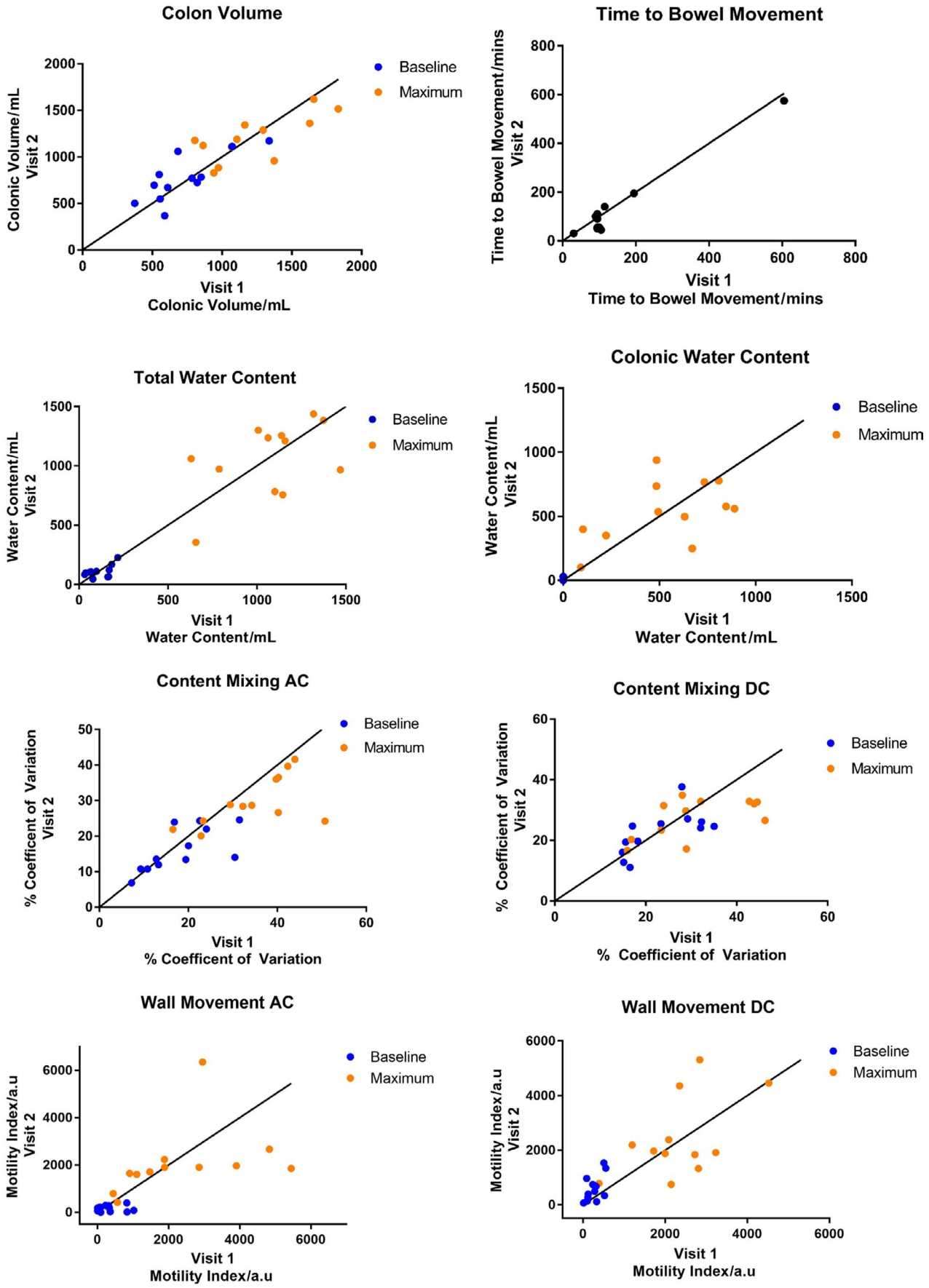

FIGURE 4 Correlation all endpoints at baseline and maximum, with line of identity shown, visit 1 vs visit 2

motion was multiplied with the normalized luminal diameter changes to generate a plot highlighting both deformation (expansion and contraction) and motion of the bowel wall. The area under this plot above a threshold value (which excluded breathing noise artifacts in the data) was then calculated.

2.6 | Statistical analysis

Basic characteristics of the study population were summarized using frequencies, percentages, means and standard deviations as appropriate. The maximum value after the drink for each MRI parameter was determined from T60 and T120 data for each subject to allow for the fact that oro-cecal transit times of the drink, and hence time of peak colonic distension, could differ between the two visits. Normality of data was assessed using the D'Agostino and Pearson normality test, and all statistical tests were performed using GraphPad Prism version 7.03 for Windows (GraphPad Software).

The reproducibility of these MRI parameters (volumes, water content, content mixing and wall movement) as well as time to first bowel movement (TBM) was determined by carrying out Bland-Altman analysis.[21] Coefficients of variation ((Standard Deviation/Mean) × 100) for intrasubject data and ICC (using two way mixed models with absolute agreement) were calculated for the baseline and maximum values acquired by $T = 120$ minutes from starting the drink, analyzed from the two visits. Intersubject coefficient of variance data was also assessed to determine whether the intrasubject variability was similar to the intersubject variability.

Bland-Altman plots were generated with dotted lines representing bias and 95% limits of agreement, and a paired *t* test or Wilcoxon test (if non-normal data) was used to assess the statistical significance of this bias. For ICC, the 95% confidence interval of the ICC estimate is used as the basis to evaluate the level of reliability using the following general guideline:

> Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability.[22]

We also looked at the use of a "responder rate" to assess the wall movements response to the stimulus, using the 90% centile of baseline values as a cut off for a definition of "responder"; we determined whether participants responded to the macrogol stimulus the same way on both occasions. This follows the assumption that the baseline data represent the no or very low motility state with its inherent measurement error due to breathing and positioning of the lines to generate the motility metric. A 90% limit to this baseline data would therefore give a realistic upper limit to the no motility state. Response to stimulus was also tested in all MRI endpoints at both visits using either the paired *t* test or Wilcoxon test of baseline and maximum values, to determine whether a significant increase in each endpoint was measured after the macrogol drink.

This was a pilot study to enable us to make power calculations for the MRI endpoints for future studies. Given the expense of these studies, we chose a sample size of 12 which we felt was a reasonable compromise and has some justification based on rationale around feasibility and precision of estimates.[23] A previous manometry reproducibility study showed good reproducibility in ambulatory manometry readings with just seven participants.[9]

3 | RESULTS

Twelve participants were recruited: nine female, three male, mean age 26 (SD 5) and body mass index 24.8 (SD 3.2) kg/m. Examples of images obtained for analysis are shown in Figure 2, highlighting the features extracted from the MRI data.

3.1 | Reproducibility measures

The details of the summary data for our MRI endpoints and TBM as well as coefficients of variation and ICC are shown in Table 1. All MRI endpoints changed significantly from baseline to maximum values following the macrogol challenge (Table 1).

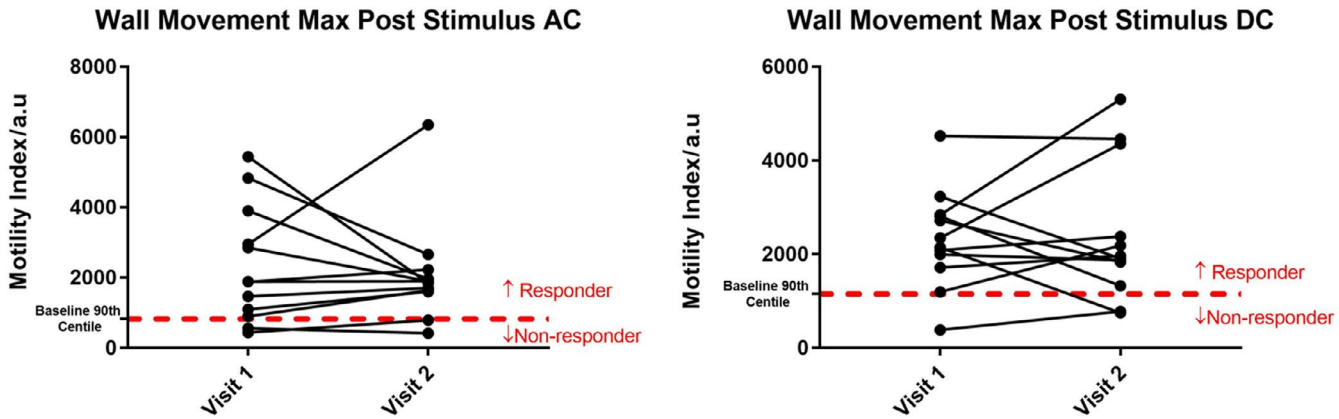

FIGURE 5 Graph of responders/non-responders for colonic wall movement

For all endpoints, the intrasubject CoV was smaller than the intersubject CoV. The ICCs were more varied with all the ICC's above 0.6 (moderate); however, some of the lower limits of the 95% CI dropped to 0.3. The ICC for volumes and water content performed best with colonic volume ICC at 0.84, and maximum total gut water content and maximum colonic water content were 0.92 and 0.85, respectively. Reproducibility for mixing and movement measurements of both the contents and walls in both the AC and DC performed less well (ranged from 0.62 to 0.76). The time to bowel movement had an ICC of 0.98.

Bland-Altman plots are shown in Figure 3 for the maximum post-stimulus data only, which show no statistically significant bias in the data; however, the 95% limits of agreement varied greatly. Correlation graphs of baseline and maximum values, with line of identity shown, visit 1 vs visit 2, are shown in Figure 4 and show the large effect of the macrogol stimulus on the MRI endpoints measured.

3.2 | Responder rate

Using the 90% centile of baseline values as a cutoff for a definition of "responder" to the stimulus, the results of the individual peak values with a responder line for both AC and DC wall movement are shown in Figure 5. This shows that for the AC, all participants kept their responder status and in the DC one participant changed responder status across visits.

3.3 | Symptom scores

Symptom scores for abdominal pain, flatulence and bloating were all low. All participants scored zero at baseline for all symptoms. For both visits at T60 and T120, median scores were all <0.5 for all symptoms. There was no significant difference found between visit 1 and 2 scores for any symptoms at both time points (p values between $P = .44$ and $P > .9$, Wilcoxon test).

4 | DISCUSSION

Our results indicate that colonic volumes, content mixing and wall movement all consistently increased above baseline post-stimulus. This is consistent with previously published data on healthy volunteers using different quantities of the macrogol challenge drink.[5,6,17] MRI endpoints showed large intersubject variability with coefficients of variation across the cohort ranging from 33% to 94%. Importantly, the intrasubject variability was lower than the intersubject variability for all endpoints measured (range 11%-85%). This means that all individuals' data had more in common with itself than with the group as a whole.

The colonic volume and AC content mixing data had good intrasubject reproducibility. Fasting colonic volumes have already been shown to be consistent on different occasions[24,25]; however, the fact that these volume and content mixing measurements were also reproducible post-stimulus suggests that these responses are relatively consistent and change quite slowly over the measurement time. This is particularly the case for the AC content mixing measurement, a dynamic flow measurement, also known as tagging, which is effectively acquired for just 40 seconds (20-seconds acquisition with a gap of 1 hour). If this content mixing was more erratic, a bigger variation in the data would be observed. In addition to this, by allowing a maximum value of the response to be used in this protocol, it has removed some of the variation that changes in oro-cecal transit time between visits could introduce, which would in turn impact on the response of the colon to the stimulus.

AC and DC wall movement were reasonably repeatable at baseline, with a low metric measured compared to the post-stimulus data, but the response to the challenge was variable between study days resulting in a lower ICC overall and indicating variability in the physiological response to the stimulus, likely due to the irregular nature of colonic contractions following the macrogol drink. It is known from manometry data that in resting condition, colonic contractions are erratic; a study in healthy volunteers performed over 4 hours found that high amplitude contractions make up only 1.4% of the contractile activity of the colon.[26] Simultaneous detection of these high amplitude contractions from manometry with MRI has been previously shown by Kirchhoff et al[27] who also showed low motility in their basal data prior to bisacodyl instillation in the DC. They also showed that following the bisacodyl not all subjects' colons produced high amplitude contractions during their 24-minute measurement period, with some subjects producing multiple contractions and others none at all. Given the fact that the wall movement scanning acquisition time was just 10 minutes each scan session, it perhaps is not that surprising that larger variability was found for these data using this method. The contractions seen in the wall of the AC and DC following the macrogol drink are not continuous, but sporadic and will depend on several factors. These would include the rate of delivery of the macrogol to the AC, mixing of the macrogol with the colonic contents already present, and the absorption rate of any fluid from the macrogol. All these factors will influence the distension of the colon wall which is probably the main trigger for the wall motion observed. The water content measurements showed there was larger variability of this measure, across the two visits, compared to the colonic volumes (although individual colonic segments showed larger variation [Table S1]) and colonic content mixing, again supporting the assumption of variable oro-cecal transit of the macrogol to the colon and its subsequent transport and absorption.

However, with our definition of responder (ie, those whose post-stimulus response was greater than the 90% centile of baseline values defining the "no motility" state), all subjects kept the same status for AC wall movements and only one changed for DC across visits. The DC definition of responder was set higher than the AC due to larger amounts of movement present during the baseline scan for this region of the colon. There is also more susceptibility of the DC to artifacts from the motion in the neighboring small bowel which may erroneously increase the index. Since intra- and inter-individual variability in baseline motility were very similar, we felt it reasonable to use a single threshold of 90% of group values rather than expressing response as a fixed % change from individual baseline. This approach

is likely to be used in clinical practice when looking for abnormalities in motility in patient populations.

The time to first bowel movement also showed low variability across the visits; however, it is worth noting that due to the nature of the study days patients were more likely to go in the half-hour periods they had between scans, and no participants needed to go while in the scanner itself (or at least did not ask to be taken out the scanner mid scan) which constrains the data to limited values and may artificially improve its reproducibility. This parameter has obvious face validity and is highly relevant to patient management; however, although a useful objective clinical measure, it does not define the abnormality of colonic function. Being a large stimulus, it overcomes the uncontrolled variability in baseline values to yield a value which is highly reproducible compared to baseline parameters. It could be useful as a screening test to determine who would benefit from the more expensive and detailed MRI test. While our procedures at present may be too demanding for routine clinical use, we believe a single scan assessing colonic volume and colonic wall movement at 60 minutes could provide a cost-effective way of excluding colonic inertia but this would need testing in a future study that evaluated the impact of our test as part of a care pathway.

This study was limited by the relatively small sample size, especially as the data are so heterogeneous, and other factors such as diet in the preceding days were not controlled, and this could have had an impact on the baseline state of the bowel resulting in larger variability. Equally the data were only collected over a relatively short period (within either breath holds or over 10 minutes for the wall movements), and it is possible that these time periods are not representative of the overall effect. In comparison, data collected from the traditional manometry techniques can record from 2- to 4-hour up to a 24-hour period; however, this is impractical for MRI studies. Non-dietary standardization of the baseline condition was carried out (only fasting and restricting exercise, alcohol and caffeine consumption) due to impracticalities of undertaking a dietary approach in clinical practice. Variable transit times of constipation patients would mean that dietary interventions prior to the scan day may influence some patients more than others. In addition, requesting defecation prior to starting the scanning would be of limited use as almost all of the constipation patients would not be able to comply. Some of the variability seen in the measurements may have come from intra-observer variability in the analyses of the data. This source of variation in the measurements was beyond the scope of the study. Previous limits of agreement data for water content measurements have been measured at −11% to 13% (interobserver) and −4% to 3% (intra-observer),[16] and for total colonic volumes, interobserver variation is around 5% (unpublished data). However, intra-observer and interobserver variations will be an important determinant for the use of the individual MRI parameters in future studies and as a clinical test and will be investigated in future studies. The dose of macrogol drink was adjusted to subject weight because of our prior experience that smaller people could not tolerate the full 1 L. We felt that habitual intake would be proportional to weight rather than height, and hence, tolerance also affected by weight. In any event, the doses chosen were well tolerated with median abdominal pain and bloating <0.5 on our 0-3 scale, but acknowledge this approach may have led to some variability in the colonic stimulus.

In conclusion, the colonic response to the macrogol challenge as assessed by MRI is heterogeneous but large compared to baseline data and has moderate to good reproducibility, making it a suitable test to study potential pathologies underlying GI disorders such as constipation. More data are needed to better define the normal range for comparison with patient groups who may have both hypo- and hypermotile responses to the challenge drink, and the reproducibility of the test in patients will also need investigating.

We anticipate that this test could be of value by providing an objective measure of responsiveness of the colon to the macrogol stimulus. It may be particularly valuable in showing that the colon is not inert in patients who are dissatisfied with their response to standard therapies. This would be of value in the work up of patients in whom colectomy is being considered and encourage a more vigorous search for behavioral abnormalities like pelvic dyssynergia or eating disorders which can be missed in routine care.

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CONFLICT OF INTEREST

RS has received research funding from Norgine and Zespri. He has also acted on advisory boards for Allergan, Commonwealth Diagnostics International, Napo Pharmaceuticals, Ipsen, and Yuhan and received speakers' fees from Menarini and Alfawasserman. AM is the CEO of Motilent Limited, a medical imaging analysis company. MC has acted as a consultant for Allergan and Kiowa Kirin, and DA has received research support from Philips. ST is a research consultant for Robarts and holds share options in Motilent. The remaining authors have no COI to declare.

AUTHOR CONTRIBUTIONS

CH, RS, PG, LM, ST, DA, and MC designed the research. CH and VWS recruited the participants. VWS and CB collected the data. VWS, AM, and CH analyzed the data, and CC provided statistical support. VWS and CH wrote the manuscript draft. All authors revised the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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