

# Detecting the effects of a standardized meal challenge on small bowel motility with MRI in prepared and unprepared bowel

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## Abstract

**Objective:** MRI is increasingly used to evaluate small bowel contractility. The objective of this study was to validate a clinically practical stimulation test (300-kcal meal) for small bowel motility.

**Methods:** Thirty-one healthy subjects underwent dynamic MRI to capture global small bowel motility after  $\pm 10$ h fasting, of which 15 underwent bowel preparation consisting of 1 L 2.5% mannitol solution and 16 did not. Each subject underwent (1) a baseline motility scan (2) a food challenge (3) a post-challenge scan, and (4) second post-challenge scan (after  $\pm 20$  minutes). This protocol was repeated within 2 weeks. Motility was quantified using a validated motility assessment technique.

**Key Results:** Motility in prepared subjects at baseline was significantly higher than motility in unprepared subjects (0.36 AU vs 0.18 AU,  $P < 0.001$ ). In the prepared group, the food challenge produced an 8% increase in motility ( $P = 0.33$ ) while in the unprepared subjects a significant increase of 30% was observed ( $P < 0.001$ ). Responses to food remained insignificant ( $P = 0.21$ ) and significant ( $P = 0.003$ ), for the prepared and unprepared subjects, respectively,  $\pm 20$  minutes post food challenge. These results were confirmed in the repeated scan session.

**Conclusion & Inferences:** A significant response to a 300-kcal meal was measured within 10 minutes in unprepared bowel, supporting the clinical use of this challenge to provoke and assess motility changes. A caloric challenge did not produce an observable increase in motility in mannitol prepared subjects.

## KEYWORDS

dynamic MRI, food challenge, motility, small bowel, stimulation test

## 1 | INTRODUCTION

Our understanding of gastrointestinal diseases has expanded rapidly, but advances in how we assess functional impairments have

remained a clinical challenge. One of the main suspected contributors to the symptom burden in gastrointestinal diseases is impaired motility but we simply do not have widely available tests to assess this process. Gastroduodenal manometry, for example,

**Abbreviations:** bFFE, Balanced Fast Field Echo; CIPO, Chronic Intestinal Pseudo-obstruction; IBS, Irritable Bowel Syndrome; LoA, Bland-Altman 95% limits of agreement; MMC, Migrating motor complex; MRI, Magnetic Resonance Imaging.

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is the reference standard but is expensive, invasive, and limited to specialized centers only. Various limitations can be found with other techniques making routine clinical assessment of motility challenging.<sup>1</sup>

Increasingly, MRI has been used as a methodology in research to evaluate contractility within the small bowel.<sup>1,2</sup> MRI is non-invasive, safe and widely available and, coupled with advances in post-processing technologies, enables rapid and repeatable quantification.<sup>3-11</sup> Encouragingly, the first steps toward clinical implementation have been taken with dynamic motility imaging now being routine in various centers and with several prospective clinical studies being published.<sup>3-19</sup>

The gastrointestinal tract is complex, undergoing fasted and fed contractile cycles that take place over hours, such as the migrating motor complex.<sup>20</sup> It is not practical to perform prolonged MRI imaging of the intestine in a clinical setting. A stimulus challenge would be helpful to introduce a degree of predictability into a clinical testing (akin to cardiac stress testing with adenosine<sup>21</sup>) to trigger a gastrointestinal response within a short time frame and allow pre and post comparisons which may become altered in disease. Importantly, such a stimulus test would be robust to intrinsic baseline variation between subjects which we know is quite high.<sup>22</sup>

The purpose of this study is therefore to develop such a stimulus protocol that might be used clinically to evaluate gastrointestinal dysmotility. We use a 300-kcal meal challenge to produce a “physiological” response (rather than a pharmacological one) that might more closely mirror the drivers of many gastrointestinal symptoms but at the same time be reactively tolerable to subjects. Routine clinical preparation for gastrointestinal MRI consists of ingestion of a near-zero-calorie fluid with large volume, for bowel distention and contrast.<sup>23</sup> This was used in many of the previous MRI motility studies, but this preparation fluid likely already stimulates motility. Hence, in this study, the stimulation test was validated in both prepared and unprepared subjects to evaluate the stimulation test and provide guidance on MRI preparation for future MRI motility studies.

## 2 | MATERIAL AND METHODS

### 2.1 | Ethical

Data were collected at Amsterdam UMC, location Academic Medical Center (AMC), University of Amsterdam, The Netherlands. Ethical permission was obtained from the relevant Medical Ethics Committee (NL54884.018.15) and all subjects gave full written informed consent.

### 2.2 | Volunteers

Thirty-one healthy subjects were recruited prospectively by advertisement and interview. Inclusion criteria included healthy, human volunteers who were willing to undergo minimal bowel preparation and MRI. Exclusion criteria were contraindications to undergo MR imaging, age younger than 18 years or older than 45 years, history

### Key Points

- MRI is increasingly used to evaluate small bowel motility both in research and clinical practice. In this study, we develop a MRI stimulation test for GI motility assessment and performed this in mannitol prepared and unprepared bowel.
- A response to a 300-kcal meal can be seen within 10 minutes in unprepared bowel with dynamic MRI. Additionally, mannitol, a near-zero calorie, large volume, bowel preparation produced significantly higher motility than seen in fasted subjects, for the first time demonstrating the motility-driving effect of mannitol.
- This study provides new insights into MRI quantified small bowel motility assessment. It shows MRI can be used to quantitatively evaluate small bowel motility changes to a physiological meal stimulus in a clinically practical time frame, establishing baseline motility values in mannitol prepared and unprepared healthy subjects. These results will serve as a baseline for upcoming studies in a range of patient groups.

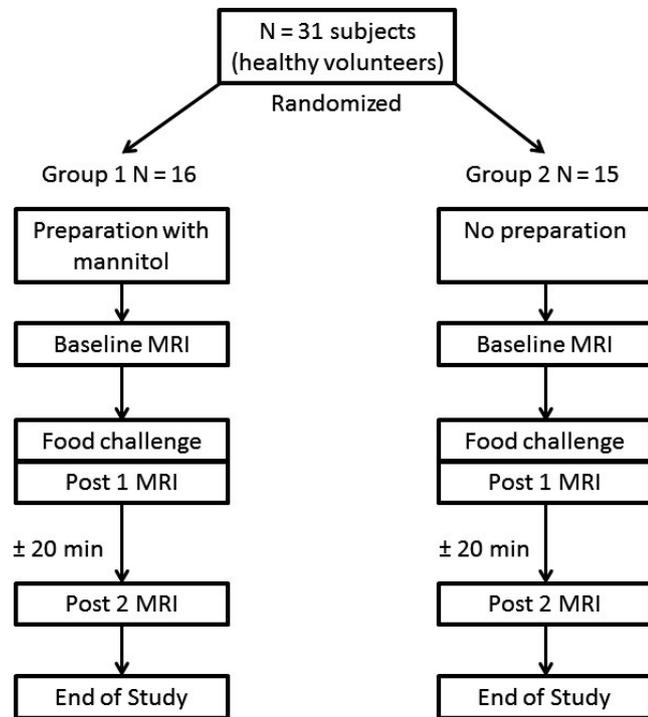
of abdominal surgery, gastrointestinal diseases, or current gastrointestinal symptoms.

### 2.3 | Study design

All volunteers underwent dynamic MRI in the morning to capture global small bowel motility after a  $\pm 10$  hours overnight fast. The cohort was randomly split into two, (1) a bowel prepared and (2) an unprepared group. The 15 subjects in the prepared group ingested 1 L of 2.5% mannitol solution (routine clinical preparation<sup>23</sup>) prior to the scan session. The unprepared subjects received no preparation. Each subject thereafter underwent the same MRI protocol with (1) a baseline motility scan followed by (2) a food challenge (3) a post-challenge scan immediately after the food challenge, and (4) a second post-challenge scan (after approximately 20 minutes). See Figure 1 for the study design flowchart. This protocol was repeated within 2 weeks (mean: 7 days, SD: 1.5 days). The test meal was administered within a few minutes, as fast as the volunteer was able to drink it. Volunteers were asked to maintain their usual diet. To keep ingestion conditions similar between the two scan sessions, the volunteers kept a food diary 24 hours before the first scan and were asked to follow this diary again the 24 hours before the second scan session.

### 2.4 | MRI protocol

Scans were acquired with a 3T Philips Ingenia MRI scanner (Philips, Best, the Netherlands) in supine position using a combination of a posterior coil located in the table and an anterior torso coil covering



**FIGURE 1** Study design flowchart of one scan session

the entire abdominal region. After the initial survey sequences, a coronal single slice 2D Balanced Fast Field Echo (bFFE) motility sequence of the bowel was acquired. The motility scan was acquired during an expiration breath-hold, and the volunteers were instructed to hold their breath for approximately 20 seconds. The scan parameters were: TE/TR: 0.98/1.90 ms, flip angle: 20°, FOV: 400 × 400 mm<sup>2</sup> (FH × LR), spatial resolution: 2.5 × 2.5 × 10 mm, resulting in a temporal resolution of 10 frames per second (fps), also referred to as images per second.

## 2.5 | Test meal

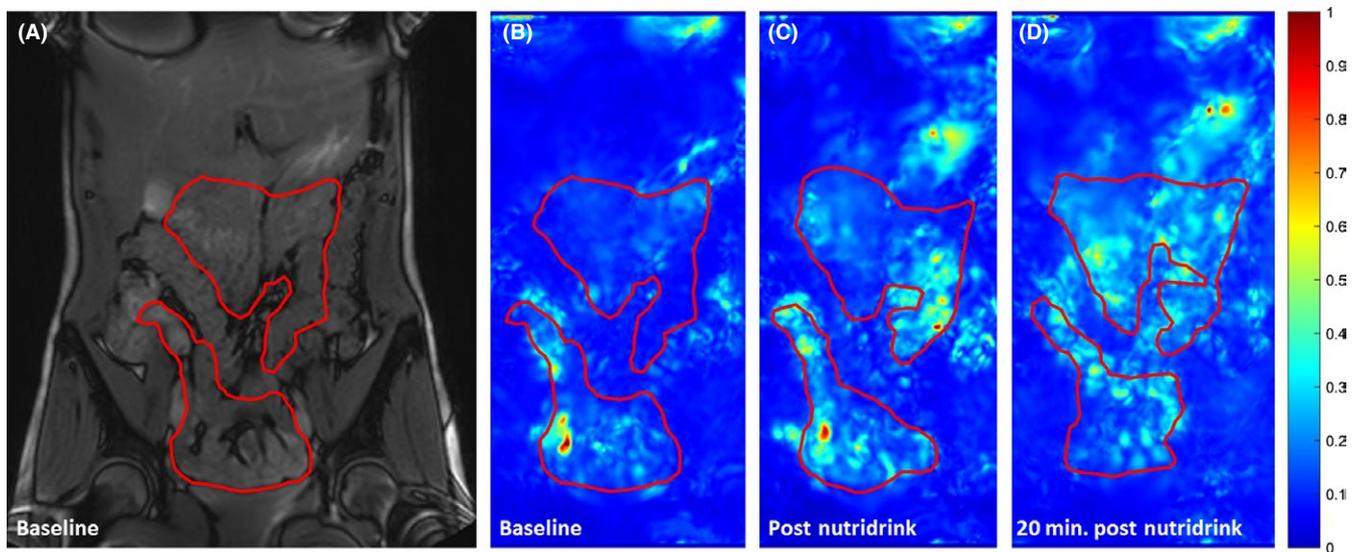
The standardized test meal used for the food challenge was a bottle of 200 mL Nutridrink (Juice style, apple flavor, N.V. Nutricia, Zoetermeer, The Netherlands), consisting of 300 kcal energy per bottle. The nutrient content of the meal/100 mL was: energy 150 kcal, protein 3.9 g, carbohydrate 33.5 g, and fat 0 g. This meal was chosen for its well tolerated and calorie dense content, expected to induce the postprandial phase and therefore increase motility.

## 2.6 | Motility analysis

Motility was quantified within a ROI delineating the entire small bowel (Figure 2A), using a validated motility assessment technique GIQuant™ (Motilent, Ford, UK).<sup>7</sup>

Each dynamic series was registered with GIQuant™ to produce a series of deformation fields which can be summarized by taking the standard deviation of each deformation field's Jacobian determinant for the time series. This measure was previously validated<sup>22</sup> as a robust surrogate for motility and can be depicted visually as a color map (Figure 2B-D) and henceforth referred to as the motility index (expressed in arbitrary units [AU]).

Motility data visualization and secondary analysis was performed in MATLAB 2016 (The MathWorks, Natick, MA, USA). This included a graphical user interface that displayed the dynamic series datasets as a movie as well as a static reference image and allowed for ROI placement. A global ROI was manually drawn for each subject in the static reference image by KLR. The global ROI segmented the entire small bowel visible in a slice, if possible other abdominal structures like the mesentery were not included. The delineations were checked, and adjusted if needed, by experienced investigators CSJ and JS in consensus.



**FIGURE 2** The registration target image used for the small bowel annotations (A) and the resulting motility maps (B-D) where blue = low motility and green/red = high. The baseline motility is visualized in (B), the motility directly after the food challenge is visualized in (C) and the motility ±20 minutes later is visualized in (D)

## 2.7 | Statistical analysis

The motility index is presented as median and inter-quartile range. All data were checked first for normality to confirm the use of non-parametric statistical tests. Baseline motility between groups was compared using a Wilcoxon rank-sum test. Change of motility from baseline to the two measurements after the food challenge within groups was compared using a Friedman test and, in case of significance, further investigated using a Wilcoxon signed-rank test. Additionally the median effect size (% change) of the food challenge was calculated for the latter. This was done by subtracting the baseline motility from the post Nutridrink motility and dividing this by the baseline motility multiplied by 100. Effect size between groups was compared using a Wilcoxon rank-sum test. The analyses were performed on the data from scan session A, the data from scan session B was used for reproducibility analysis.

Reproducibility of the motility measurements was illustrated by using Bland-Altman plots, and quantified using 95% limits of agreement (LoA) and intraclass correlation (ICC 2). Intra-subject agreement was determined by calculating the within-subject coefficient of variation (%). This was calculated by dividing the within-subject standard deviation motility by the group mean motility multiplied by 100. Smaller scores reflect greater reproducibility.

All statistical analyses were performed using Rstudio (Rstudio Inc., Boston, MA, USA). To correct for multiple testing we applied a Bonferroni correction, therefore *P*-values below 0.005 are considered statistically significant.

## 3 | RESULTS

Thirty-one healthy subjects were included (15 females, median age 23 [range 19-37 years], median BMI 21.7 [range 18.8-30.1], median

fasting time 604 minutes [range 432-764 minutes]), the preparation, and scan protocols were well tolerated and no adverse effects were observed. One subject did not attend the second (reproducibility) measurement and was therefore excluded from the reproducibility analysis. Due to a technical problem with the MRI scanner, the post 1 scan of one volunteer could not be measured in both scan sessions; this was addressed as a missing value in statistical testing.

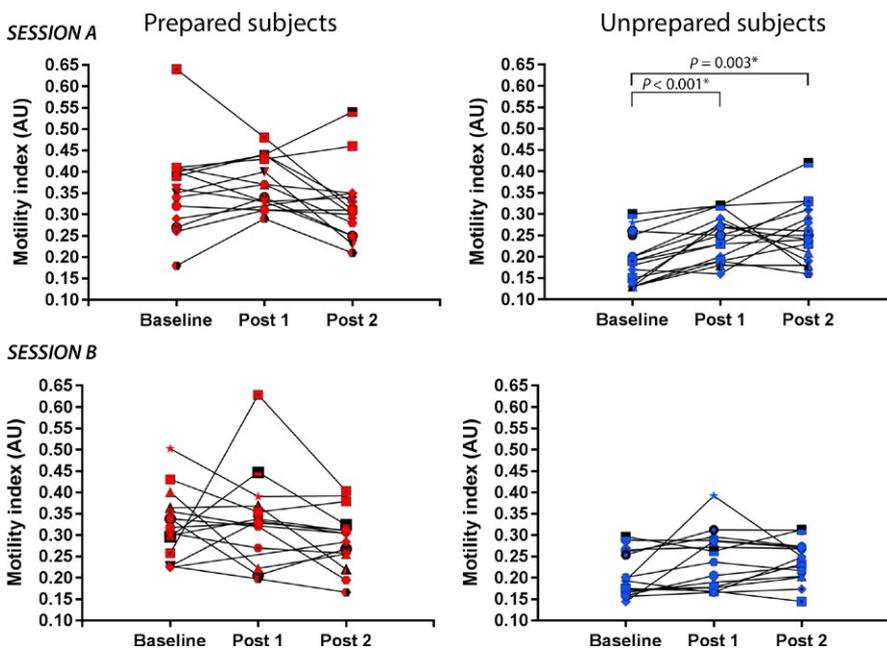
### 3.1 | Mannitol prepared vs. unprepared volunteers

Figure 3 illustrates measured motility in the first and second MRI session at baseline, directly after the food challenge (post 1) and  $\pm 20$  minutes after the challenge (post 2). Figure 3, session A, depicts how motility in prepared subjects at baseline was significantly higher than motility in unprepared subjects at baseline (0.36 AU vs 0.18 AU,  $P < 0.001$ ), similar differences can be seen in the measurements directly after scanning (0.37 AU vs 0.25 AU,  $P < 0.001$ ) and  $\pm 20$  minutes after scanning (0.31 AU vs 0.24 AU,  $P = 0.03$ ). These data are summarized in Table 1.

### 3.2 | Response to food

The color maps in Figure 2, visually demonstrate the response to the food challenge in one subject; Figure 3 represents all the motility measurements. In the prepared group, the food challenge produced an 8% insignificant increase in motility ( $P = 0.33$ ), nine of fifteen subjects showed an increase in motility. In the unprepared subjects, a significant increase of 30% was observed ( $P < 0.001$ ), fourteen of sixteen subjects showed an increase in motility. This effect was significantly different between the prepared and unprepared group ( $P = 0.002$ ).

Responses  $\pm 20$  minutes post food challenge compared to baseline remained insignificant in the prepared group ( $P = 0.21$ ) and significant in the unprepared group ( $P < 0.001$ ). This effect was significantly different between the prepared and unprepared group



**FIGURE 3** Global small bowel motility in prepared subjects (left) and unprepared subjects (right) at baseline, directly after the food challenge (Post 1) and  $\pm 20$  minutes after the food challenge (Post 2). Measured at session A and 1-2 weeks later at session B

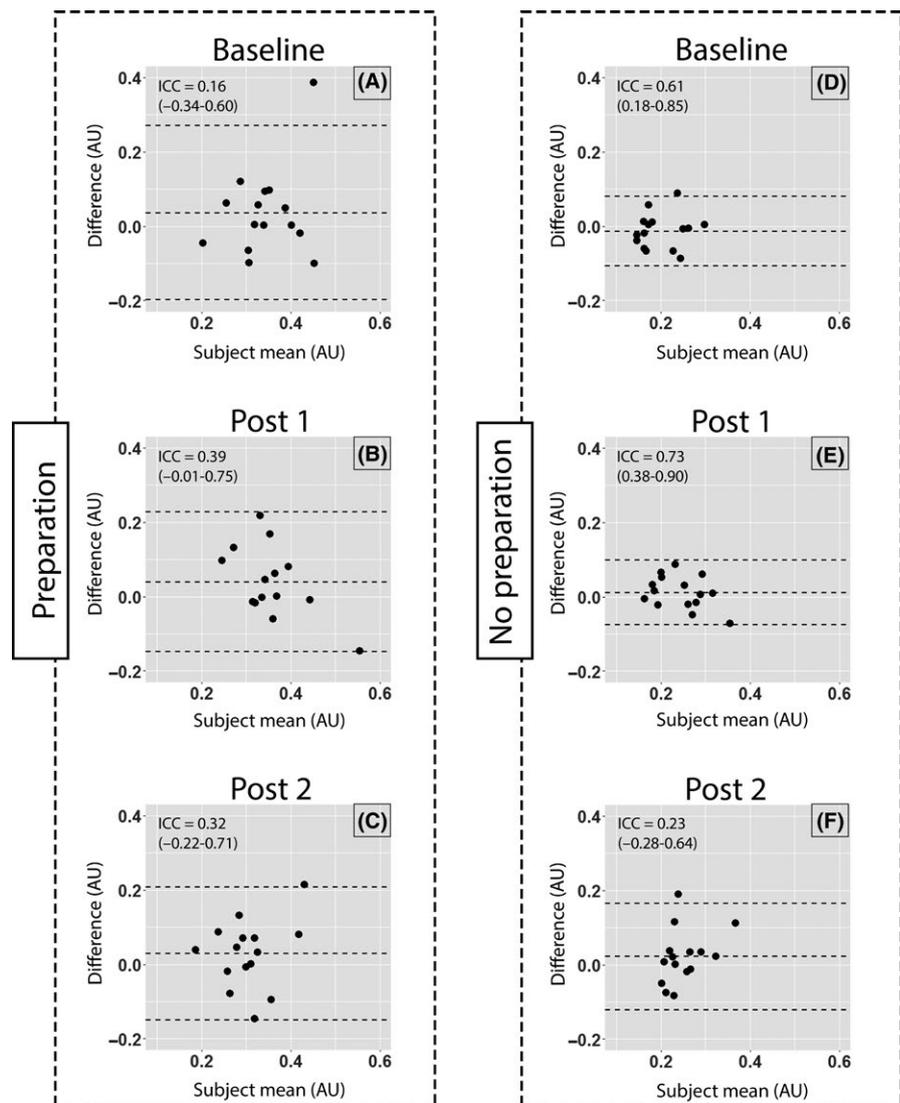
**TABLE 1** Median and inter-quartile range of the motility index (in arbitrary units) of both the prepared and unprepared group in session A and B at baseline, directly after the food challenge (post 1) and  $\pm 20$  minutes after (post 2). Differences between groups were calculated using the Wilcoxon rank-sum test. Significance is represented with an asterisk (\*)

	Session A Median (Q1-Q3, SD)		P-value (between groups)	Session B Median (Q1-Q3, SD)		P-value (between groups)
	Prepared	Unprepared		Prepared	Unprepared	
Baseline	0.36 (0.31-0.40, 0.10)	0.18 (0.14-0.21, 0.06)	<0.001*	0.32 (0.28-0.36, 0.08)	0.19 (0.17-0.26, 0.05)	<0.001*
Post 1	0.37 (0.33-0.44, 0.06)	0.25 (0.20-0.28, 0.05)	<0.001*	0.33 (0.28-0.37, 0.11)	0.24 (0.18-0.29, 0.07)	0.003*
Post 2	0.31 (0.27-0.35, 0.09)	0.24 (0.21-0.29, 0.07)	0.030	0.30 (0.26-0.32, 0.07)	0.25 (0.21-0.27, 0.05)	0.050

( $P < 0.001$ ). In the prepared group, an insignificant decrease in motility was observed  $\pm 20$  minutes after the food challenge compared to the motility directly after the food challenge ( $P = 0.025$ ), 11 subjects showed a decrease in motility. This effect was not significantly different between the prepared and unprepared group ( $P = 0.05$ ). These data are visualized in Figure 3.

### 3.3 | Reproducibility

Comparing the two scan sessions, the mean difference (intra-subject variation) between the baseline motility was 0.037 AU in the prepared group and  $-0.013$  AU in the unprepared group (Figure 4A and D). The mean difference between motility directly after drinking



**FIGURE 4** Bland-Altman limits of agreement and intraclass correlation (95% confidence interval) between baseline motility, directly after food (Post 1), and  $\pm 20$  minutes after food (Post 2) in the mannitol prepared (A-C) and unprepared group (D-F)

was 0.040 AU in the prepared group and 0.012 AU in the unprepared group (Figure 4B and E). The mean difference between motility  $\pm 20$  minutes after drinking was 0.029 AU in the prepared group and 0.022 AU in the unprepared group (Figure 4C and F). Intra-class correlations varied between 0.16 and 0.73 (Figure 4) without significant differences between the prepared and unprepared groups since all 95% confident intervals overlap.

For baseline motility, the within-subject coefficient of variation was 34.6% in mannitol prepared subjects vs 23.7% in unprepared subjects. Directly after the food challenge, this was 26.7% vs 18%, respectively. and  $\pm 20$  minutes after the food challenge this was 29.8% vs 29%, respectively.

Regarding the measurement of response to the food stimulus, described above for session A, similar results are found in session B (Figure 3).

## 4 | DISCUSSION AND CONCLUSION

In this study, we demonstrate that a 300-kcal test meal significantly increased motility in fasted subjects within 10 minutes of MRI scanning. Conversely, ingesting this test meal could not produce a significant effect on the small bowel motility in mannitol prepared subjects. These results were confirmed in the repeat session, demonstrating that a simple food stimulus may be used as an efficacious challenge to observe contractile response in the unprepared small bowel with MRI. Furthermore, mannitol, a near-zero calorie but large volume bowel preparation substance, already significantly increased motility itself in fasted subjects and no further increase was measured after ingestion of the test meal.

There are fundamental differences between the gastrointestinal motility patterns in the fasted (interdigestive) and fed (postprandial) state that can be measured.<sup>24,25</sup> Assessing the transition between these states and demonstrating an abnormal response can provide information on pathophysiology, and aid in diagnosis and patient management. Our study demonstrates that MRI allows assessment of the fasted to fed transition, providing the additional ability to assess the response in the duodenum, jejunum, and ileum in a clinically practical timeframe. Finding the appropriate kind of stimulus for clinical response testing to explore complex functional disease is the key challenge and one that requires further research following on from this study. Even though we used a simple nutritionally balanced challenge here, a range of nutrient combinations might be investigated to suit different indications especially in patients with dietary triggered GI symptoms.

In as little time as 10 minutes we measured significant response which concurred with the findings by Khalaf et al. who performed a similar MRI experiment over 270 minutes and found a maximum motility response immediately after ingestion of a test meal.<sup>26</sup> Patients with gastrointestinal motility and functional bowel disorders frequently experience symptoms after ingestion of food and a food provocation test might enable us to explore this reaction further in a range of conditions and diseases.<sup>16,27,28</sup> In the case of treatment,

response testing could be useful as monitoring tool or inclusion/exclusion criteria to improve the homogeneity of the cohort of interest.

Our final results explore reproducibility and showed that there is a relatively large intra-subject spread between motility scans across the two time-points. Even though the inter-subject (population) variation of the baseline scan in the mannitol prepared group compare well to results in a previous study<sup>22</sup>, we see a relative large difference in the intra-subject variation. This might be explained by the fact that we only measured motility on one 2D slice compared to the motility obtained by Menys et al.<sup>22</sup> by averaging the motility of fifteen slices of a 3D volumetric scan. Additionally, this variation in baseline measurements in the unprepared group can be explained by the variation of the contractile activity in the fasted (interdigestive) phase driven by the migrating motor complex (MMC).<sup>20</sup> This being said, the variation with relation to the anticipated effect size seen in result to, for example, a spasmolytic agent is not very high. In the study by Menys et al.<sup>22</sup> the effect of butylscopolamine was a 57% decrease in motility, representing by mean motility difference of 0.17, so we need to interpret these findings in the context of the clinical effect size of interest. It is possible that it can be explained by a variation in the response to mannitol between people or the response to the test meal which was itself relatively small. Meanwhile, the consistent significance of the response measurement in the unprepared group appears convincing. These findings place even more emphasis on the stimulation protocol being necessary in MRI based dysmotility research. It is likely that the young healthy volunteers in our study display low variation, but motility ranges in CIPO patients will vary greatly<sup>16-18</sup> and applying this test in a disease group will help contextualize our findings.

Although not the principle question addressing this study, our results firmly support that a side effect of oral preparation in healthy subjects is stimulation of gastrointestinal motility, pushing the motility toward the range of the fed state. Reassuringly, these results are comparable to the motility measured in a previous study with twenty, mannitol prepared, healthy subjects (mean index 0.34; range, [0.28-0.39]), supporting the validity of our results.<sup>22</sup> This motility-driving effect of mannitol is interesting because it can be used to our advantage in clinical testing bringing into relief regions of hypo-motile intestine potentially affected by inflammation or fibrosis.<sup>12-14,19,29-32</sup> Similarly, tethered regions of bowel, due to adhesions or fistulae, might also be highlighted by the general increase in motility driven by the effects of mannitol. From a practical perspective, a series of breath-hold scans in mannitol prepared subjects are compatible with clinical scanning and they are increasingly performed as part of clinical practice primarily in IBD clinics.

This study had limitations. We used relatively short acquisition times, only  $\pm 20$  seconds per measurement. These breath-hold acquisitions ensured that only bowel motion was captured and no breathing influenced our acquisitions, but if breathing can be filtered out, longer free-breathing acquisitions (eg, minutes instead of seconds) can provide more motility information. Our study population is relatively small and homogeneous. Further research in disease groups is required to see if patients can tolerate the study

protocol. Additionally, mannitol prepared bowels delineate easier and therefore faster than unprepared bowels due to the contrast in the scans. For the purpose of this study, we chose to analyze the global motility of the small bowel. However, a diversity of metrics might be essential to explore different features of gastrointestinal motility, indicating an important future aspect of this research field.

This study provides new insights into MRI quantified small bowel motility assessment, establishing baseline motility values in mannitol prepared and unprepared healthy subjects and describing a significant response after a food challenge in unprepared healthy subjects. In order to validate the clinical value of these motility measurements, more people need to be measured and the test needs to be validated in several disease groups.

In conclusion, the rapid response to calories (<10 minutes) detected with a dynamic MRI stimulation test in unprepared bowel suggests this test may be useful for clinical application and supports further development.

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## CONFLICT OF INTEREST

AM is the Founder and CEO of Motilent Ltd., a medical imaging analysis company. JS is research consultant for Robarts Clinical Trials on MRI in Crohn's disease.

## AUTHOR CONTRIBUTIONS

CSJ, KLR, and JS performed the research; CSJ, AJN, and JS designed the research study; AJB contributed essential insights on the study design; CSJ and AM analyzed the data; AM contributed the essential post-processing tool; AJB contributed insights on the interpretation of the results; CSJ and AM wrote the manuscript; AJB, AJN, and JS revised the manuscript.

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