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Colon wall motility: comparison of novel quantitative semiautomatic measurements using cine-MRI

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Key Words:	Cine MRI, motility, imaging metric, ascending colon

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1 2	Colon wall motility: comparison of novel quantitative
3	semi-automatic measurements using cine-MRI
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5	Running title: Colonic Wall Motility using cine-MRI
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26	CC acquired the data, AM, VH, DA, and SAT developed the registration

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algorithms and designed the analysis interface, CLH, AM, KM analysed the data.

CLH, AM, LM, GM, RCS, SAT and PAG interpreted the data. CLH and AM drafted

the manuscript. CLH, AM, LM, RCS, SAT and PAG critically reviewed the

manuscript. All authors approved the final version.

2 3	1	ABSTRACT
4 5 6	2	Background: Recently cine MRI has shown promise for visualising movement of
7 8	3	the colonic wall, although assessment of data has been subjective and observer
9 10	4	dependent. This study aimed to develop an objective and semi-automatic
11 12	5	imaging metric of ascending colonic wall movement, using image registration
13 14	6	techniques.
15 16	7	Methods: Cine balanced turbo field echo (bTFE) MRI images of ascending
17 18 19	8	colonic motility were acquired over 2 minutes from 23 healthy volunteers (HVs)
20 21	9	at baseline and following <mark>two different macrogol stimulus drinks (11 HVs drank</mark>
22 23	10	1L and 12 HVs drank 2 L). Motility metrics derived from large scale geometric
24 25	11	and small scale pixel movement parameters following image registration were
26 27	12	developed using the post-ingestion data and compared to observer grading of
28 29 20	13	wall motion. Inter and intra-observer variability of the highest correlating metric
30 31 32	14	was assessed using Bland-Altman analysis calculated from 2 separate
33 34	15	observations on a subset of data.
35 36	16	Key Results: All the metrics tested showed significant correlation with the
37 38	17	observer rating scores. Line analysis produced the highest correlation coefficient
39 40	18	of 0.74 (95% CI 0.55-0.86), p<0.001, (Spearman Rho). Bland-Altman analysis
41 42 42	19	of the inter <mark>-</mark> and intra-observer variability for the line analysis metric, showed
43 44 45	20	almost zero bias and small limits of agreement between observations (-0.039-
46 47	21	0.052 intra-observer and -0.051-0.054 inter-observer, range of measurement 0-
48 49	22	0.353).
50 51	23	Conclusions and Inferences: The line analysis index of colonic motility derived
52 53	24	from cine MRI registered data provides a quick, accurate and non-invasive
54 55 56	25	method to detect wall motion within the ascending colon following a colonic
57 58	26	stimulus in the form of a macrogol drink.

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2	Keywords: Cine MRI, motility, imaging metric, ascending colon
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4	Key Messages
5	
6	Recent cine MRI has shown promise to visualise the movement of the colonic
7	walls, however assessment has been limited to subjective and semi-automatic
8	analysis.
9	
10	This study reports the development of an objective metric of ascending colon
11	motility derived from cine MRI data using image registration techniques to
12	remove respiratory motion and parameterise bowel movements.
13	
14	Data from 23 healthy volunteers, who had received a macrogol stimulus, were
15	used to assess potential metrics, which were derived from cine MRI data. These
16	metrics were compared to an observer score of motility.
17	
18	The line analysis metric produced the highest correlation coefficient with the
19	observer scoring. Inter- and intra-observer variability was low for this metric.
20	
21	This study has shown <mark>that</mark> it is possible to generate objective semi-automatic
22	metrics of colonic motility from cine MRI data using image registration
23	techniques.
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2 3 4	1	Assessment of colonic motor activity is difficult owing to its erratic nature and
5 6	2	the inaccessibility of the colon for study. Previous methods have largely relied on
7 8	3	procedures that are unpleasant for patients and demanding for staff; these
9 10	4	involve placing pressure probes into the colon, which usually requires bowel
11 12	5	cleansing, colonoscopy and often endoscopic clips to secure the probe,
13 14	6	facilitating long term recordings (1). Recent developments with high resolution
15 16	7	manometry have provided unprecedented detail on the different types of motor
17 18 10	8	activity (2) but the technique remains difficult and expensive, limiting use to a
20 21	9	few specialised centres. Scintigraphic methods allow accurate, reproducible
22 23	10	assessment of transit and have been widely used to investigate pharmacologic
24 25	11	modulation of gut transit (3). However scintigraphy only assesses bulk transit
26 27	12	and does not allow detailed assessment of the motor patterns which may be
28 29	13	relevant when studying disease or drugs which specifically target abnormal
30 31	14	motility. More recently the Smart Pill has been introduced as a less invasive
32 33	15	alternative while still allowing direct assessment of motor activity (4). Although
34 35 36	16	better tolerated by patients, its use is limited by expense and it cannot be used
37 38	17	to reliably assess specific regions of the colon because of the inability to control
39 40	18	its position. This is also the case for the proposed Magnetic Tracking System (5)
41 42	19	which again relies on the passage of a magnetic pill through the GI tract to
43 44	20	assess the motor activity. Increasing data suggests dynamic motion capture
45 46	21	"cine" MRI is acceptable to patients and could allow detailed evaluation of colonic
47 48 40	22	motor activity. It has previously been shown that 1 litre of electrolyte macrogol
49 50 51	23	solution provides a reliable stimulus with vigorous movements of the ascending
52 53	24	colon (AC) in healthy volunteers (6) within an hour of ingestion. MRI scanners
54 55	25	are now widely available in larger hospitals and costs for a short examination
56 57		
58 59		

(30 minutes) are similar to those of a nuclear medicine gastric emptying test and are considerably less than endoscopy and colonoscopy.

An important component to MR based motility assessment is automation and quantitative analysis, and non-linear image registration based techniques (7) can provide a range of quantitative measures for assessing bowel motion. Registration provides 1) parametric surrogate markers of motility and 2) allows automatic propagation of regions of interest (ROIs) through time series data once an ROI has been defined on a single image (7). This type of analysis has produced objective and repeatable metrics of global small bowel motility (8, 9). Until recently, the most widely used registration technique was only applicable to breath-held data (8, 10) as breathing produces additional motion within the images that is not related to the GI motion of interest, thus confounding the data, by mimicking bowel movement. This is problematic for colonic motility imaging as contractions are comparatively infrequent necessitating free-breathing protocols. Recent advances however have introduced a dual stage process that first corrects respiratory motion in extended free-breathing data sets (11) before performing motility assessment (12) facilitating data collection of longer time periods. Colonic motion has been recently studied using cine MRI (6, 13, 14), but analysis remains subjective and time consuming using semi-quantitative, subjective assessment of contractions, flow and bowel wall motion. To date there have been no reported investigations of objective imaging metrics of colonic motility derived from free breathing MRI data.

25 The aim of this study was to develop an objective imaging metric which

26 quantifies movement in the ascending colon walls during free breathing cine

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1 MRI, by applying image registration techniques to generate the metrics and validate these against observer rating scores of motility. 2 3 4 Materials and Methods 5 6 The data used for this work was a subset of that acquired from an open-label, 7 parallel group design study in healthy volunteers using MRI to investigate the 8 small bowel and colonic response to 1 and 2 litres of polyethylene glycol (PEG) (Macrogol 3550) electrolyte solution (Moviprep[®], Norgine Pharmaceuticals Ltd, 9 10 Harefield, UK) (6). Such PEG solutions are widely used in larger quantities than 11 used here as bowel cleansing preparations prior to colonoscopy or barium enema 12 examinations. The full study was registered on the EU Clinical Trials Register 13 with EudraCT Number 2010-021879-85. It was approved by the National 14 Research Ethics Service (approval 10/H0906/50), the NHS Trust R&D (approval 15 10GA018) and by the Medicines and Healthcare products Regulatory Agency 16 (MHRA Clinical Trial Authorization CTA 03057/0045/001-0001, protocol 10050). 17 All volunteers gave written consent before participating. 18 The details of the study protocol have been already published (5). In brief 24 19 healthy volunteers were divided into two age matched groups of 12 subjects. 20 Group 1 received 1 litre of PEG electrolyte solution at 1pm on day 1 following a 6 21 hour fast and a further 1 litre at 8am the next morning. Group 2 were given a 22 single dose of 2 litres PEG electrolyte solution at 8am on the study day following 23 an overnight fast. Group 1 was given 1 hour to ingest the solution and Group 2 24 was given 2 hours. Time 0 was then defined as the time of the first MRI scan 25 immediately after ingestion of the PEG electrolyte solution. Baseline scans 26 (performed according to the protocol described below) were acquired before the

PEG electrolyte solutions were ingested and then further scans were acquired hourly for 4 hours following ingestion. Subjects spent around 15-20 minutes in the scanner at each time point and sat upright for the rest of the time. 1 subject from Group 1 withdrew from the study. To provide a range of motility data, only the baseline and first two post ingestion time points were considered (baseline, T=0, T=60 min). To identify potential motility metrics, the post-ingestion data from group 1 and group 2 were combined to provide a range of motility responses as it has previously been shown that the motility response (assessed by an observer) was dose dependent (6).

Imaging was carried out using a 1.5 T Philips Achieva Scanner. Each volunteer was positioned supine in the scanner with a 4 element parallel imaging body coil wrapped around the abdomen. The colonic motility scan was one of a range of scans acquired to characterise the response of the gastrointestinal tract to the PEG solution; information on all the sequences used can be found in (6). The colonic motility scan comprised of a single sagittal slice, balanced turbo field echo (bTFE) positioned by the radiographer centrally through the AC with field of view 330 x 228 mm², in-plane resolution 1.5 x 1.5 mm, slice thickness 15 mm, flip angle 70°, repetition time/echo time 3.0/1.5 ms. A cine dataset was acquired using this sequence every second for 2 minutes. Subjects were asked to shallow breath throughout the acquisition.

The data was registered using the DRAM methodology (12) performed at a
different laboratory, blind to the subject preparation. In brief, effects of
respiratory motion on the data were first removed by registering using Robust

26 Data Decomposition Registration(11). The resulting images were then

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2 3 4	1	subsequently non-linearly registered using an optic flow technique (7) to
5 6	2	generate the deformation fields which define how each image maps onto a
7 8	3	median image generated from the entire data series.
9 10	4	
11 12	5	Following registration, in-house software written using ${\sf Matlab}^{{ m B}}$ (The Mathworks
13 14	6	Inc) was used to allow an observer to define regions of interest (ROI) and lines
15 16	7	across the single median image of the AC (Figure 1). This information was then
17 18 19	8	used to automatically derive both small scale pixel-based and large scale
20 21	9	geometry-based metrics, from the registration parameters.
22 23	10	
24 25	11	Four potential imaging metrics were investigated, two based on small scale pixel
26 27	12	deformation fields and two based on large scale geometry changes. A single
28 29 20	13	observer (CH) defined all the ROIs to generate the different metrics.
30 31 32	14	(A) SD_JAC : The standard deviation (SD) of the Jacobian, representing the
33 34	15	fractional area change of each pixel due to deformation, averaged over an
35 36	16	ROI encompassing the whole AC (drawn by an observer), a measure
37 38	17	which has previously been used to quantify small bowel motility (8). Each
39 40	18	image in the time series is registered to a target image, so that each pixel
41 42	19	has a displacement field associated with it for each time point. Distortions
43 44 45	20	that do not result in a local change of area have a Jacobian value of 1. If
46 47	21	the local area decreases, the value of the Jacobian will decrease towards
48 49	22	zero and if the area expands its value will increase above 1. Therefore,
50 51	23	when we report a SD Jacobian of 0.34 for a given pixel we are saying that
52 53	24	for 68% of time points, the total fractional area change falls within 0.34
54 55	25	units of 1 (with 1 being no displacement). The larger the SD Jac the
วช 57 58	26	greater the variation in fractional area and hence more movement of the

1	pixels. SD_JAC, generated pixel by pixel (through the time series), was
2	averaged over a ROI drawn by an observer covering the whole AC to
3	generate the metric. Example maps of SD_JAC are shown in figure 2A
4	(B) SD_I : The standard deviation of the variation in intensity, linked to flow
5	due to movement of the colonic contents generated by wall movement.
6	SD_I generated pixel by pixel was averaged over a ROI drawn by an
7	observer covering the whole AC.
8	(C) LA: Line analysis index. The AC was divided into three regions (bottom-
9	section including cecum, mid-section and top-section up to the hepatic
10	flexure) and in each region an observer drew either 3 or 5 lines
11	perpendicular to the main axis of the AC, depending on the overall length
12	of the AC (Figure 1a). These lines were automatically propagated through
13	the time series using the deformation fields from the registration and the
14	length of each line at each time point was saved for subsequent analysis,
15	giving between 9 and 15 time series. The time series were smoothed
16	using a moving average of 5 data points. Example smoothed time series
17	are shown in figure 2B. For additional visualisation of motility, colour
18	motility plots were generated of (a) absolute difference in length from
19	mean for points along AC against time (Figure 2C) and (b) change in
20	length between consecutive time points (wall velocity- Figure 2 D). A
21	series of LA Motility Indices were defined as the percentage of the time
22	series line analysis data which had a change in length (i.e. wall velocity)
23	between consecutive time points of greater than 0.25, 0.5 and 0.75 ${\sf mms}^{-1}$
24	after smoothing (LA _{0.25mms⁻¹} , LA _{0.5mms⁻¹} and LA _{0.75mms⁻¹}).
25	(D) NAC: The Normalised Area Change across the time series was
26	defined by first splitting the AC into three regions of interest (ROIs)

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1	(Figure 1b) drawn by an observer; 3 regions were chosen to help identify
2	smaller wall movements which may have been missed if using a large ROI
3	of the whole AC. The ROIs were then automatically propagated through
4	the time series data using the deformation fields defined during
5	registration and the areas of the ROIs were plotted against time, and the
6	resulting time course was smoothed using a moving average of 5 points.
7	Each time course was normalised to its mean value and the number of
8	time points which were more than 3, 5 and 10% different from the mean
9	were counted and summed over all 3 regions to give three NAC Motility
10	Indices (NAC _{3%} , NAC _{5%} and NAC _{10%}).
11	These different measures were compared to an observer rating which was
12	carried out on the raw, unregistered data. The Observer Rating Score (6) was
13	defined as the duration of wall motion multiplied by the number of sections of
14	the ascending colon showing motion (with the AC being divided into 3 sections).
15	Thus if motion was observed involving the whole AC for 15 seconds and later
16	involving only 1 third of the AC for 20 seconds the corresponding observer rating
17	score would be $(15 \times 3)+(20 \times 1) = 65$ in units of segment x s. This was
18	estimated by a single observer (CH). This measure was used as the comparator
19	as it had shown to differentiate between low and high motility previously (6).
20	Motility plots using the LA data were used to define the different types of
21	contractions observed.
22	
23	Inter and intra-observer variations of the highest correlating metric were
24	obtained from data acquired by 2 observers (CH with over 15 years experience
25	of analysing GI MR images and KM with 4 years experience) and 1 observer on 2
26	occasions (CH) with the analysis separated by a 3 month period, respectively.

1	Observers were required to draw on the median image only of <mark>a subset of the</mark>
2	total data (N=33 from 11 subjects) and all subsequent analysis and generation
3	of the metrics were automated. KM was shown how to interact with the analysis
4	software (i.e. draw regions on the anatomy, save outputs etc.) by CH.
5	
6	As a demonstration of the utility of the best correlating metric to differentiate
7	between different colonic motor activity, the differences over time (including
8	baseline data) between the two different macrogol stimuli (1L and 2L) were
9	investigated. Previous manually observed scoring of this data showed distinct
10	differences with time and between the stimuli. (6).
11	
12	Statistics
13	Statistical analysis was carried out using SPSS 20.0 (IBM) and GraphPad Prism
14	6.0 (GraphPad Software, La Jolla California USA). All data were tested for
15	normality using the Shapiro-Wilks test.
16	
17	As the observer rating score was non-normally distributed, all potential metrics
18	were correlated to it using Spearman Rho correlation coefficients, statistical
19	significance was set at $p < 0.05$. The parameter with the highest correlation to
20	the observer rating score was then used <mark>to determine the observer variability of</mark>
21	the measurement.
22	
23	To assess the inter and intra-observer variability, Bland-Altman limits of
24	agreement between observers were calculated (15) and correlation between
25	observations was assessed by the intra-class correlation coefficient.
26	

1	Results
2	After registration to remove respiratory motion, a small amount of data still
3	showed large scale movements of the whole abdomen, which when registered
4	using the optic flow technique, translated into large changes in the images not
5	associated with specific motion of the bowel. This mis-registration led to errors
6	in the metrics generated due to additional global distortions of the anatomy
7	(from respiratory motion) producing large scale changes to the deformation
8	fields, and hence overestimating motility. Data sets which showed large scale
9	breathing distortions on the images post registration were excluded from
10	subsequent analysis. These were identified using organs such as the liver and
11	kidney which should normally be static after image registration to correct for
12	respiration. As a result 7 data sets (15 %) were excluded from post-ingestion
13	data and a further 4 data sets (17 %) from the baseline data.
14	
15	Demographics of the subject groups used for metric correlation and inter-
16	observer measurements are given in Table 1. Example images and 2D motility
17	plots are shown in Figure 2. All proposed measures showed significant
18	correlation with the observer rating scoring, however only a few metrics
19	(SD_JAC and line analysis) showed highly significant correlation ($p < 0.01$) and
20	this is summarised in Table 2 and Figure 3. The normalised area change indices
21	and SD_I showed very weak correlation with the observer rating score. The
22	$LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices showed the highest correlation with the observer
23	rating score and this metric was therefore investigated for the inter- and intra-
24	observer measurements.
25	

1	The line analysis plots of displacement and velocity also provided additional
2	information as to the types of contractions seen following this stimulus.
3	Examples of the different types of contractions are shown in Figure 4. Using the
4	plots to define the contractions, there were 5 types of contractions seen:
5	segmental antegrade and retrograde contractions, whole AC antegrade and
6	retrograde contractions and near simultaneous large amplitude contractions.
7	The last type of contraction appears to significantly change the whole lumen
8	diameter rapidly and over a very short period of time (typically < 20 s). All these
9	types of contraction could be visually seen by observing the cine data if
10	displayed as a movie. Dilation of the lumen was also observed on many of the
11	datasets (Figure 4 B and C).
12	
13	Inter and intra-observer Bland-Altman measurements and Intra-class correlation
14	coefficients are summarised in Table 3 for the $LA_{0.25mms^{-1}}$ and $LA_{0.5mms^{-1}}$ indices
15	These data show that there was very little bias between observations for the
16	inter- and intra-observer measurements of line analysis with small limits of
17	agreement compared to the range of values measured (limits of agreement
18	Inter-obs $LA_{0.5mms^{-1}}$: -0.051 to0.054, range of measurement: 0.000-0.353)
19	Intra-class correlation coefficients were statistically significant (and coefficients
20	above 0.9) for both LA indices calculated.
21	
22	The variation of the colonic motility activity (as assessed with $LA_{0.5mms^{-1}}$ index)
23	with both time and macrogol stimulus is shown graphically in Figure 5. Baseline
24	motility was low compared to the post-stimulus data, with the 2 L having a
25	larger effect immediately after ingestion.
26	

1	
2	Discussion
3	This study has shown that objective metrics of ascending colon motility can be
4	generated non-invasively with minimal observer input using cine MRI combined
5	with registration techniques. The line analysis (LA) indices proved to be the most
6	robust measures of those examined, correlating well with the subjective scoring
7	of wall movement (6). In addition the motility plots of wall deformation and wall
8	velocity allowed a quick visual assessment of any contractions including smaller
9	movements which were occurring, in a similar way to pressure changing maps
10	generated by high resolution manometry. Five different types of contraction
11	were observed both visually, and from the motility plots, following the macrogol
12	stimulus, both segmental over short distances in the AC as well as encompassing
13	the whole AC region. Retrograde and antegrade and near simultaneous wall
14	movements were observed and were a result of the colonic response to the large
15	fluid content from the stimulus drink. These contractions were probably induced
15 16	fluid content from the stimulus drink. These contractions were probably induced to aid mixing and absorption the fluid within the chyme. The most common type
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15 16 17 18 19 20 21 22 23 24 24 25 26	fluid content from the stimulus drink. These contractions were probably induced to aid mixing and absorption the fluid within the chyme. The most common type of wall movement was segmental retrograde, however it is beyond the scope of this paper to define all the contractions observed throughout the datasets. By using image registration to correct for breathing effects, data could be acquired over extended time periods, without any additional observer analysis time needed. The recording period of 2 minutes used in this study could be extended to allow more sporadic motility patterns to be investigated. The imaging sequences are available on all modern scanners hence the technique could be widely used in clinical practice. As colonic wall movement occurs on a longer time scale than a breath hold (2) the image registration is important if these methods are to be of clinical use. Typical computing time for the registration for

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a 2 minute cine-MRI dataset would be 15 mins, with observer drawing and

metric calculations taking a further 2-3 minutes. In comparison manual

assessment of the motility from a single 2 minute cine could take up to 10

minutes, depending on the number of contractions present, and this would

reflecting the objective nature of this registration-based approach which is

contractions which can be detected over a short recording period. Different

amounts of ingested fluid, elicit different responses, with the tendency of larger

amounts of fluid to initially stimulate more wall movement. A previous study by

high amplitude propagation pressure waves as defined by manometry when the

data are acquired simultaneously. They also noted that MRI showed increases in

luminal diameter which were not detected by the manometry probe, as already

observed by Wright et al (16) who carried out simultaneous measurements in

the stomach. This increased sensitivity to wall activity provided by MRI, may

mixing its contents and propelling them towards the rectum. Recent work using

high resolution manometry by Dinning et al (17, 18) has shown that the motor

patterns within the colon are far more complicated than previously thought, and

interpretation of the actual motor patterns. Cine MRI with image registration

could now provide an alternative, non-invasive approach to viewing the colonic

provide a greater understanding of the physiology of the colon in terms of

the crude spacing of conventional manometry sensors resulted in mis-

Kirchhoff et al (14) demonstrated that MRI is extremely accurate in detecting

This study showed that an influx of fluid into the AC stimulates rapid

increase with longer acquisition periods. Inter and intra-observer variability was

extremely low, with excellent correlation between the 2 measurements acquired,

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crucial for clinical practice.

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walls. This could provide further information on the basic physiology of the colon, without disturbing the natural environment. This technique can also be extended to other segments of the colon and in defining objective clinical information in constipation patients. Further studies are needed to determine both optimal timings of MRI assessment of colonic motility following PEG ingestion and the optimal volume of stimulating drink to ingest. However it could be envisaged that a protocol similar to that used for MR imaging of the small bowel in Crohn's disease could be developed. Subjects would arrive at the MRI unit and be given the stimulating drink. A period of time later they would have a short 20-30 minute MRI scan where measurements of colonic motility could be made. There are limitations to the proposed technique. The validation of the metrics was based on observer scores of motility and is therefore not a 'gold standard' measure for comparison although the observers did have extensive experience of imaging the colon using MRI. However it is also possible that the computer algorithm will detect motion in the colon not visualised by the observer. The line analysis metric showed good consistency across different subjects with a wide range of observed motility scores. Acquisition of the data is currently from a single slice positioned within the AC and thus results could be influenced by poor positioning of the slice, or anatomy which is not easily visualised in a single plane. Multislice acquisition, to gain greater coverage of the anatomy, is possible with reduced temporal or spatial resolution and would allow investigation of other less straight colonic regions such as the descending and sigmoid colon. Over estimation of motility from imperfect registration of the data occurred, if the raw data showed large movements of all internal organs from respiration.

1	From the subjects studied here 14-18% of the data was corrupted with mis-
2	registration errors and was discarded. However in future studies, these errors
3	can be minimised by training of the subjects to breath in a shallow manner
4	during data acquisition and with active monitoring of the data collected; an
5	approach not available with this data, which was looked at retrospectively. It is
6	also possible that other more sophisticated metrics may provide greater
7	correlation to the motility seen in the AC; however a simplistic approach was
8	taken for this study to allow fast generation of the metrics studied.
9	
10	In conclusion the line analysis index of colonic motility derived from cine MRI
11	registered data provides a quick, accurate and non-invasive method to detect
12	wall motion within the ascending colon following a colonic stimulus in the form of
13	a macrogol drink.
14	
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17	Health Research Biomedical Research Unit. The views expressed are those of the
18	authors and not necessarily those of the NHS, the NIHR or the Department of
19	Health.
20	
21	AM is a director and shareholder of Motilent Ltd. All other authors have no
22	conflicts of interest to disclose.
23	
24	Abbreviations:
25	AC – Ascending colon
26	bTFE – balanced Turbo Field Echo

- HV – Healthy volunteers
 - LA – Line analysis
 - MRI Magnetic Resonance Imaging
 - NAC – Normalised Area Change
 - PEG - polyethylene glycol
 - ROI – Region of Interest
 - SD_JAC – Standard deviation of the Jacobian
 - SD_I Standard deviation of Intensity

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1 Tables

23 Table 1. Demographics of the two subject groups, data presented as mean (std)

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	Total Cohort (N=23)	Inter-observer Group (N=11)
Gender M / F	<mark>11/12</mark>	<mark>3/8</mark>
Mean Age (yrs)	<mark>27.1 (8.5)</mark>	<mark>26.7 (10.2)</mark>
Age Range (yrs)	<mark>19-50</mark>	<mark>20-50</mark>
BMI (kgm ⁻²)	<mark>23.2 (2.4)</mark>	<mark>23.2 (2.3)</mark>

1 Table 2. Correlation of potential metrics with the observer rating score.

	Post Ingestion N	<mark>= 39</mark>	
Metric	Spearman Rho	95% Confidence	<mark>p-value</mark>
	correlation	interval of coefficient	
SD_JAC	<mark>0.492</mark>	<mark>0.199-0.704</mark>	<mark>0.002</mark>
SD_I	<mark>0.368</mark>	0.050-0.619	0.021
LA _{0.25mms-1} Index	<mark>0.673</mark>	<mark>0.447-0.819</mark>	<mark><0.001</mark>
LA _{0.5mms-1} Index	<mark>0.739</mark>	<mark>0.545-0.858</mark>	<mark><0.001</mark>
LA _{0.75mms-1} Index	<mark>0.649</mark>	<mark>0.411-0.804</mark>	<mark><0.001</mark>
NAC _{3%} Index	<mark>0.366</mark>	0.047-0.617	0.022
NAC _{5%} Index	<mark>0.353</mark>	0.032-0.608	0.028
NAC _{10%} Index	0.329	0.006-0.590	0.041

- Table 3. Bland-Altman Limits of Agreement and Intra class correlation
- 3 coefficients for intra- and inter-observer measurements of the LA metrics

4 (N=33).

				1		
Metric	Intra-o	bserver		Inter-o	bserver	
(range of						
observation 1)	Bias	95% Limits of	ICC	Bias	95% Limits of	ICC
,		Aareement			Aareement	
	0 014		0 981	_		0 956
(0, 0, 0, 0, 6, 25)	0.014	-0.0+0-0.07+	*	0 005	-0.090-0.005	*
(0.009-0.023)	0.007	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.004	0.005		0.047
LA _{0. 5mms-1} Index	0.007	-0.039-0.052	0.964	0.001	-0.051-0.054	0.947
(0.000-0.353)			*			*
* p<0.001						

1	Figure Legends
2	
3	Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line
4	analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index
5	
6	Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of
7	standard deviation of Jacobian. Original data as insert. (B) Example single
8	smoothed line length plot from mid AC. (C) Wall displacement motility plots from
9	line analysis, colour bar indicates change in length of smoothed line length from
10	mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive
11	line lengths after smoothing.
12	
13	Figure 3. Graphs showing correlation between motility metrics and observer
14	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility
14 15	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index.
14 15 16	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index.
14 15 16 17	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis
14 15 16 17 18	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions –
14 15 16 17 18 19	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C)
14 15 16 17 18 19 20	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low
14 15 16 17 18 19 20 21	 rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA_{0.5 mms⁻¹} motility index, (D) NAC_{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the
14 15 16 17 18 19 20 21 22	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms} ⁴ motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared
14 15 16 17 18 19 20 21 22 23	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.
14 15 16 17 18 19 20 21 22 23 23 24 25	rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA _{0.5 mms⁻¹} motility index, (D) NAC _{5%} motility index. Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.

2 3	1	due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3
4 5 6	2	2L; T=60 mins: N=1 1L, N=1 2L.
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Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index 90x59mm (300 x 300 DPI)



Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of standard deviation of Jacobian. Original data as insert. (B) Example single smoothed line length plot from mid AC. (C) Wall displacement motility plots from line analysis, colour bar indicates change in length of smoothed line length from mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive line lengths after smoothing.
 148x199mm (300 x 300 DPI)



Figure 3. Graphs showing correlation between motility metrics and observer rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA_{0.5 mms-1} motility index, (D) NAC_{5%} motility index. 95x60mm (300 x 300 DPI)



Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde

contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C.

180x156mm (300 x 300 DPI)





Figure 5. Box and whisker plot showing the variation of LA_{0.5 mms-1} with both time and macrogol stimulus. Groups N=11 1L drink, N=12 2L drink. Missing data due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3 2L; T=60 mins: N=1 1L, N=1 2L. 85x82mm (300 x 300 DPI)

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2	Colon wall motility: comparison of novel quantitative
3	semi-automatic measurements using cine-MRI
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5	Running title: Colonic Wall Motility using cine-MRI
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7	C.L. Hoad ^{1,2*} , A. Menys ³ , K. Garsed ² , L. Marciani ^{2,4} , V. Hamy ³ , K. Murray ¹ , C.
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25	Author Contributions: CLH, LM, GM, RCS and PAG designed the study, KG, and
26	CC acquired the data, AM, VH, DA, and SAT developed the registration

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2 3 4	1	algorithms and designed the analysis interface, CLH, AM, KM analysed the data.
5	2	CLH, AM, LM, GM, RCS, SAT and PAG interpreted the data. CLH and AM drafted
7 8	3	the manuscript. CLH, AM, LM, RCS, SAT and PAG critically reviewed the
9 10	4	manuscript. All authors approved the final version.
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1 ABSTRACT

Background: Recently cine MRI has shown promise for visualising movement of
the colonic wall, although assessment of data has been subjective and observer
dependent. This study aimed to develop an objective and semi-automatic
imaging metric of ascending colonic wall movement, using image registration
techniques.

7 Methods: Cine balanced turbo field echo (bTFE) MRI images of ascending 8 colonic motility were acquired over 2 minutes from 23 healthy volunteers (HVs) 9 at baseline and following two different macrogol stimulus drinks (11 HVs drank 10 1L and 12 HVs drank 2 L). Motility metrics derived from large scale geometric 11 and small scale pixel movement parameters following image registration were 12 developed using the post-ingestion data and compared to observer grading of 13 wall motion. Inter and intra-observer variability of the highest correlating metric 14 was assessed using Bland-Altman analysis calculated from 2 separate 15 observations on a subset of data.

Key Results: All the metrics tested showed significant correlation with the observer rating scores. Line analysis produced the highest correlation coefficient of 0.74 (95% CI 0.55-0.86), p<0.001, (Spearman Rho). Bland-Altman analysis of the inter- and intra-observer variability for the line analysis metric, showed almost zero bias and small limits of agreement between observations (-0.039-0.052 intra-observer and -0.051-0.054 inter-observer, range of measurement 0-0.353).

Conclusions and Inferences: The line analysis index of colonic motility derived
from cine MRI registered data provides a quick, accurate and non-invasive
method to detect wall motion within the ascending colon following a colonic
stimulus in the form of a macrogol drink.

		Hoad 4
1 2		
2 3 4	1	
5 6	2	Keywords: Cine MRI, motility, imaging metric, ascending colon
7 8	3	
9 10	4	Key Messages
11 12	5	
13 14 15	6	Recent cine MRI has shown promise to visualise the movement of the colonic
16 17	7	walls, however assessment has been limited to subjective and semi-automatic
18 19	8	analysis.
20 21	9	
22 23	10	This study reports the development of an objective metric of ascending colon
24 25	11	motility derived from cine MRI data using image registration techniques to
26 27	12	remove respiratory motion and parameterise bowel movements.
20 29 30	13	
31 32	14	Data from 23 healthy volunteers, who had received a macrogol stimulus, were
33 34	15	used to assess potential metrics, which were derived from cine MRI data. These
35 36	16	metrics were compared to an observer score of motility.
37 38	17	
39 40 41	18	The line analysis metric produced the highest correlation coefficient with the
42	19	observer scoring. Inter- and intra-observer variability was low for this metric.
44 45	20	
46 47	21	This study has shown that it is possible to generate objective semi-automatic
48 49	22	metrics of colonic motility from cine MRI data using image registration
50 51	23	techniques.
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Assessment of colonic motor activity is difficult owing to its erratic nature and the inaccessibility of the colon for study. Previous methods have largely relied on procedures that are unpleasant for patients and demanding for staff; these involve placing pressure probes into the colon, which usually requires bowel cleansing, colonoscopy and often endoscopic clips to secure the probe, facilitating long term recordings (1). Recent developments with high resolution manometry have provided unprecedented detail on the different types of motor activity (2) but the technique remains difficult and expensive, limiting use to a few specialised centres. Scintigraphic methods allow accurate, reproducible assessment of transit and have been widely used to investigate pharmacologic modulation of gut transit (3). However scintigraphy only assesses bulk transit and does not allow detailed assessment of the motor patterns which may be relevant when studying disease or drugs which specifically target abnormal motility. More recently the Smart Pill has been introduced as a less invasive alternative while still allowing direct assessment of motor activity (4). Although better tolerated by patients, its use is limited by expense and it cannot be used to reliably assess specific regions of the colon because of the inability to control its position. This is also the case for the proposed Magnetic Tracking System (5) which again relies on the passage of a magnetic pill through the GI tract to assess the motor activity. Increasing data suggests dynamic motion capture "cine" MRI is acceptable to patients and could allow detailed evaluation of colonic motor activity. It has previously been shown that 1 litre of electrolyte macrogol solution provides a reliable stimulus with vigorous movements of the ascending colon (AC) in healthy volunteers (6) within an hour of ingestion. MRI scanners are now widely available in larger hospitals and costs for a short examination

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(30 minutes) are similar to those of a nuclear medicine gastric emptying test
 and are considerably less than endoscopy and colonoscopy.

3

An important component to MR based motility assessment is automation and 4 5 quantitative analysis, and non-linear image registration based techniques (7) 6 can provide a range of quantitative measures for assessing bowel motion. 7 Registration provides 1) parametric surrogate markers of motility and 2) allows 8 automatic propagation of regions of interest (ROIs) through time series data 9 once an ROI has been defined on a single image (7). This type of analysis has 10 produced objective and repeatable metrics of global small bowel motility (8, 9). 11 Until recently, the most widely used registration technique was only applicable to 12 breath-held data (8, 10) as breathing produces additional motion within the 13 images that is not related to the GI motion of interest, thus confounding the 14 data, by mimicking bowel movement. This is problematic for colonic motility 15 imaging as contractions are comparatively infrequent necessitating free-16 breathing protocols. Recent advances however have introduced a dual stage 17 process that first corrects respiratory motion in extended free-breathing data 18 sets (11) before performing motility assessment (12) facilitating data collection 19 of longer time periods. Colonic motion has been recently studied using cine MRI 20 (6, 13, 14), but analysis remains subjective and time consuming using semi-21 quantitative, subjective assessment of contractions, flow and bowel wall motion. 22 To date there have been no reported investigations of objective imaging metrics 23 of colonic motility derived from free breathing MRI data.

24

25 The aim of this study was to develop an objective imaging metric which

26 quantifies movement in the ascending colon walls during free breathing cine

MRI, by applying image registration techniques to generate the metrics and
 validate these against observer rating scores of motility.

Materials and Methods

The data used for this work was a subset of that acquired from an open-label, parallel group design study in healthy volunteers using MRI to investigate the small bowel and colonic response to 1 and 2 litres of polyethylene glycol (PEG) (Macrogol 3550) electrolyte solution (Moviprep[®], Norgine Pharmaceuticals Ltd, Harefield, UK) (6). Such PEG solutions are widely used in larger quantities than used here as bowel cleansing preparations prior to colonoscopy or barium enema examinations. The full study was registered on the EU Clinical Trials Register with EudraCT Number 2010-021879-85. It was approved by the National Research Ethics Service (approval 10/H0906/50), the NHS Trust R&D (approval 10GA018) and by the Medicines and Healthcare products Regulatory Agency (MHRA Clinical Trial Authorization CTA 03057/0045/001-0001, protocol 10050). All volunteers gave written consent before participating. The details of the study protocol have been already published (5). In brief 24 healthy volunteers were divided into two age matched groups of 12 subjects. Group 1 received 1 litre of PEG electrolyte solution at 1pm on day 1 following a 6 hour fast and a further 1 litre at 8am the next morning. Group 2 were given a single dose of 2 litres PEG electrolyte solution at 8am on the study day following an overnight fast. Group 1 was given 1 hour to ingest the solution and Group 2 was given 2 hours. Time 0 was then defined as the time of the first MRI scan immediately after ingestion of the PEG electrolyte solution. Baseline scans

26 (performed according to the protocol described below) were acquired before the

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PEG electrolyte solutions were ingested and then further scans were acquired hourly for 4 hours following ingestion. Subjects spent around 15-20 minutes in the scanner at each time point and sat upright for the rest of the time. 1 subject from Group 1 withdrew from the study. To provide a range of motility data, only the baseline and first two post ingestion time points were considered (baseline, T=0, T=60 min). To identify potential motility metrics, the post-ingestion data from group 1 and group 2 were combined to provide a range of motility responses as it has previously been shown that the motility response (assessed by an observer) was dose dependent (6).

Imaging was carried out using a 1.5 T Philips Achieva Scanner. Each volunteer was positioned supine in the scanner with a 4 element parallel imaging body coil wrapped around the abdomen. The colonic motility scan was one of a range of scans acquired to characterise the response of the gastrointestinal tract to the PEG solution; information on all the sequences used can be found in (6). The colonic motility scan comprised of a single sagittal slice, balanced turbo field echo (bTFE) positioned by the radiographer centrally through the AC with field of view 330 x 228 mm², in-plane resolution 1.5 x 1.5 mm, slice thickness 15 mm, flip angle 70°, repetition time/echo time 3.0/1.5 ms. A cine dataset was acquired using this sequence every second for 2 minutes. Subjects were asked to shallow breath throughout the acquisition.

The data was registered using the DRAM methodology (12) performed at a different laboratory, blind to the subject preparation. In brief, effects of respiratory motion on the data were first removed by registering using Robust

26 Data Decomposition Registration(11). The resulting images were then

1	subsequently non-linearly registered using an optic flow technique (7) to
2	generate the deformation fields which define how each image maps onto a
3	median image generated from the entire data series.
4	
5	Following registration, in-house software written using ${\sf Matlab}^{{ m B}}$ (The Mathworks
6	Inc) was used to allow an observer to define regions of interest (ROI) and lines
7	across the single median image of the AC (Figure 1). This information was then
8	used to automatically derive both small scale pixel-based and large scale
9	geometry-based metrics, from the registration parameters.
10	
11	Four potential imaging metrics were investigated, two based on small scale pixel
12	deformation fields and two based on large scale geometry changes. A single
13	observer (CH) defined all the ROIs to generate the different metrics.
14	(A) SD_JAC : The standard deviation (SD) of the Jacobian, representing the
15	fractional area change of each pixel due to deformation, averaged over an
16	ROI encompassing the whole AC (drawn by an observer), a measure
17	which has previously been used to quantify small bowel motility (8). Each
18	image in the time series is registered to a target image, so that each pixel
19	has a displacement field associated with it for each time point. Distortions
20	that do not result in a local change of area have a Jacobian value of 1. If
21	the local area decreases, the value of the Jacobian will decrease towards
22	zero and if the area expands its value will increase above 1. Therefore,
23	when we report a SD Jacobian of 0.34 for a given pixel we are saying that
24	for 68% of time points, the total fractional area change falls within 0.34
25	units of 1 (with 1 being no displacement). The larger the SD Jac the
26	greater the variation in fractional area and hence more movement of the

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2 3	1	pixels. SD_JAC, generated pixel by pixel (through the time series), was
4 5	2	averaged over a ROI drawn by an observer covering the whole AC to
о 7 8	3	generate the metric. Example maps of SD_JAC are shown in figure 2A
9 10	4	(B) SD_I : The standard deviation of the variation in intensity, linked to flow
11 12	5	due to movement of the colonic contents generated by wall movement.
13 14	6	SD_I generated pixel by pixel was averaged over a ROI drawn by an
15 16	7	observer covering the whole AC.
17 18	8	(C) LA: Line analysis index. The AC was divided into three regions (bottom-
19 20 21	9	section including cecum, mid-section and top-section up to the hepatic
21 22 23	10	flexure) and in each region an observer drew either 3 or 5 lines
24 25	11	perpendicular to the main axis of the AC, depending on the overall length
26 27	12	of the AC (Figure 1a). These lines were automatically propagated through
28 29	13	the time series using the deformation fields from the registration and the
30 31	14	length of each line at each time point was saved for subsequent analysis,
32 33 34	15	giving between 9 and 15 time series. The time series were smoothed
35 36	16	using a moving average of 5 data points. Example smoothed time series
37 38	17	are shown in figure 2B. For additional visualisation of motility, colour
39 40	18	motility plots were generated of (a) absolute difference in length from
41 42	19	mean for points along AC against time (Figure 2C) and (b) change in
43 44	20	length between consecutive time points (wall velocity- Figure 2 D). A
45 46 47	21	series of LA Motility Indices were defined as the percentage of the time
47 48 49	22	series line analysis data which had a change in length (i.e. wall velocity)
50 51	23	between consecutive time points of greater than 0.25, 0.5 and 0.75 ${ m mms}^{-1}$
52 53	24	after smoothing (LA $_{0.25 \text{mms}^{-1}}$, LA $_{0.5 \text{mms}^{-1}}$ and LA $_{0.75 \text{mms}^{-1}}$).
54 55	25	(D) NAC: The Normalised Area Change across the time series was
56 57 58	26	defined by first splitting the AC into three regions of interest (ROIs)

(Figure 1b) drawn by an observer; 3 regions were chosen to help identify smaller wall movements which may have been missed if using a large ROI of the whole AC. The ROIs were then automatically propagated through the time series data using the deformation fields defined during registration and the areas of the ROIs were plotted against time, and the resulting time course was smoothed using a moving average of 5 points. Each time course was normalised to its mean value and the number of time points which were more than 3, 5 and 10% different from the mean were counted and summed over all 3 regions to give three NAC Motility Indices (NAC_{3%}, NAC_{5%} and NAC_{10%}). These different measures were compared to an observer rating which was carried out on the raw, unregistered data. The Observer Rating Score (6) was defined as the duration of wall motion multiplied by the number of sections of the ascending colon showing motion (with the AC being divided into 3 sections). Thus if motion was observed involving the whole AC for 15 seconds and later involving only 1 third of the AC for 20 seconds the corresponding observer rating score would be $(15 \times 3)+(20 \times 1) = 65$ in units of segment x s. This was estimated by a single observer (CH). This measure was used as the comparator as it had shown to differentiate between low and high motility previously (6). Motility plots using the LA data were used to define the different types of contractions observed.

Inter and intra-observer variations of the highest correlating metric were
obtained from data acquired by 2 observers (CH with over 15 years experience
of analysing GI MR images and KM with 4 years experience) and 1 observer on 2
occasions (CH) with the analysis separated by a 3 month period, respectively.

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1	Observers were required to draw on the median image only of a subset of the
2	total data (N=33 from 11 subjects) and all subsequent analysis and generation
3	of the metrics were automated. KM was shown how to interact with the analysis
4	software (i.e. draw regions on the anatomy, save outputs etc.) by CH.
5	
6	As a demonstration of the utility of the best correlating metric to differentiate
7	between different colonic motor activity, the differences over time (including
8	baseline data) between the two different macrogol stimuli (1L and 2L) were
9	investigated. Previous manually observed scoring of this data showed distinct
10	differences with time and between the stimuli. (6).
11	
12	Statistics
13	Statistical analysis was carried out using SPSS 20.0 (IBM) and GraphPad Prism
14	6.0 (GraphPad Software, La Jolla California USA). All data were tested for
15	normality using the Shapiro-Wilks test.
16	
17	As the observer rating score was non-normally distributed, all potential metrics
18	were correlated to it using Spearman Rho correlation coefficients, statistical
19	significance was set at $p < 0.05$. The parameter with the highest correlation to
20	the observer rating score was then used to determine the observer variability of
21	the measurement.
22	
23	To assess the inter and intra-observer variability, Bland-Altman limits of
24	agreement between observers were calculated (15) and correlation between
25	observations was assessed by the intra-class correlation coefficient.
26	

1 Results

After registration to remove respiratory motion, a small amount of data still showed large scale movements of the whole abdomen, which when registered using the optic flow technique, translated into large changes in the images not associated with specific motion of the bowel. This mis-registration led to errors in the metrics generated due to additional global distortions of the anatomy (from respiratory motion) producing large scale changes to the deformation fields, and hence overestimating motility. Data sets which showed large scale breathing distortions on the images post registration were excluded from subsequent analysis. These were identified using organs such as the liver and kidney which should normally be static after image registration to correct for respiration. As a result 7 data sets (15 %) were excluded from post-ingestion data and a further 4 data sets (17 %) from the baseline data.

Demographics of the subject groups used for metric correlation and inter-observer measurements are given in Table 1. Example images and 2D motility plots are shown in Figure 2. All proposed measures showed significant correlation with the observer rating scoring, however only a few metrics (SD_JAC and line analysis) showed highly significant correlation (p < 0.01) and this is summarised in Table 2 and Figure 3. The normalised area change indices and SD_I showed very weak correlation with the observer rating score. The LA_{0.25mms⁻¹} and LA_{0.5mms⁻¹} indices showed the highest correlation with the observer rating score and this metric was therefore investigated for the inter- and intra-observer measurements.

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The line analysis plots of displacement and velocity also provided additional information as to the types of contractions seen following this stimulus. Examples of the different types of contractions are shown in Figure 4. Using the plots to define the contractions, there were 5 types of contractions seen: segmental antegrade and retrograde contractions, whole AC antegrade and retrograde contractions and near simultaneous large amplitude contractions. The last type of contraction appears to significantly change the whole lumen diameter rapidly and over a very short period of time (typically < 20 s). All these types of contraction could be visually seen by observing the cine data if displayed as a movie. Dilation of the lumen was also observed on many of the datasets (Figure 4 B and C). Inter and intra-observer Bland-Altman measurements and Intra-class correlation coefficients are summarised in Table 3 for the LA_{0.25mms⁻¹} and LA_{0.5mms⁻¹} indices These data show that there was very little bias between observations for the inter- and intra-observer measurements of line analysis with small limits of agreement compared to the range of values measured (limits of agreement Inter-obs LA_{0.5mms-1}: -0.051 to0.054, range of measurement: 0.000-0.353)... Intra-class correlation coefficients were statistically significant (and coefficients above 0.9) for both LA indices calculated. The variation of the colonic motility activity (as assessed with $LA_{0.5mms^{-1}}$ index) with both time and macrogol stimulus is shown graphically in Figure 5. Baseline motility was low compared to the post-stimulus data, with the 2 L having a larger effect immediately after ingestion.

1	
2	Discussion
3	This study has shown that objective metrics of ascending colon motility can be
4	generated non-invasively with minimal observer input using cine MRI combined
5	with registration techniques. The line analysis (LA) indices proved to be the most
6	robust measures of those examined, correlating well with the subjective scoring
7	of wall movement (6). In addition the motility plots of wall deformation and wall
8	velocity allowed a quick visual assessment of any contractions including smaller
9	movements which were occurring, in a similar way to pressure changing maps
10	generated by high resolution manometry. Five different types of contraction
11	were observed both visually, and from the motility plots, following the macrogol
12	stimulus, both segmental over short distances in the AC as well as encompassing
13	the whole AC region. Retrograde and antegrade and near simultaneous wall
14	movements were observed and were a result of the colonic response to the large
15	fluid content from the stimulus drink. These contractions were probably induced
16	to aid mixing and absorption the fluid within the chyme. The most common type
17	of wall movement was segmental retrograde, however it is beyond the scope of
18	this paper to define all the contractions observed throughout the datasets. By
19	using image registration to correct for breathing effects, data could be acquired
20	over extended time periods, without any additional observer analysis time
21	needed. The recording period of 2 minutes used in this study could be extended
22	to allow more sporadic motility patterns to be investigated. The imaging
23	sequences are available on all modern scanners hence the technique could be
24	widely used in clinical practice. As colonic wall movement occurs on a longer
25	time scale than a breath hold (2) the image registration is important if these
26	methods are to be of clinical use. Typical computing time for the registration for

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a 2 minute cine-MRI dataset would be 15 mins, with observer drawing and metric calculations taking a further 2-3 minutes. In comparison manual assessment of the motility from a single 2 minute cine could take up to 10 minutes, depending on the number of contractions present, and this would increase with longer acquisition periods. Inter and intra-observer variability was extremely low, with excellent correlation between the 2 measurements acquired, reflecting the objective nature of this registration-based approach which is crucial for clinical practice. This study showed that an influx of fluid into the AC stimulates rapid contractions which can be detected over a short recording period. Different amounts of ingested fluid, elicit different responses, with the tendency of larger amounts of fluid to initially stimulate more wall movement. A previous study by

Kirchhoff et al (14) demonstrated that MRI is extremely accurate in detecting high amplitude propagation pressure waves as defined by manometry when the data are acquired simultaneously. They also noted that MRI showed increases in luminal diameter which were not detected by the manometry probe, as already observed by Wright et al (16) who carried out simultaneous measurements in the stomach. This increased sensitivity to wall activity provided by MRI, may provide a greater understanding of the physiology of the colon in terms of mixing its contents and propelling them towards the rectum. Recent work using high resolution manometry by Dinning et al (17, 18) has shown that the motor patterns within the colon are far more complicated than previously thought, and the crude spacing of conventional manometry sensors resulted in mis-interpretation of the actual motor patterns. Cine MRI with image registration could now provide an alternative, non-invasive approach to viewing the colonic

walls. This could provide further information on the basic physiology of the colon, without disturbing the natural environment. This technique can also be extended to other segments of the colon and in defining objective clinical information in constipation patients. Further studies are needed to determine both optimal timings of MRI assessment of colonic motility following PEG ingestion and the optimal volume of stimulating drink to ingest. However it could be envisaged that a protocol similar to that used for MR imaging of the small bowel in Crohn's disease could be developed. Subjects would arrive at the MRI unit and be given the stimulating drink. A period of time later they would have a short 20-30 minute MRI scan where measurements of colonic motility could be made.

There are limitations to the proposed technique. The validation of the metrics was based on observer scores of motility and is therefore not a 'gold standard' measure for comparison although the observers did have extensive experience of imaging the colon using MRI. However it is also possible that the computer algorithm will detect motion in the colon not visualised by the observer. The line analysis metric showed good consistency across different subjects with a wide range of observed motility scores. Acquisition of the data is currently from a single slice positioned within the AC and thus results could be influenced by poor positioning of the slice, or anatomy which is not easily visualised in a single plane. Multislice acquisition, to gain greater coverage of the anatomy, is possible with reduced temporal or spatial resolution and would allow investigation of other less straight colonic regions such as the descending and sigmoid colon. Over estimation of motility from imperfect registration of the data occurred, if the raw data showed large movements of all internal organs from respiration.

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From the subjects studied here 14-18% of the data was corrupted with mis-

registration errors and was discarded. However in future studies, these errors

can be minimised by training of the subjects to breath in a shallow manner

during data acquisition and with active monitoring of the data collected; an

also possible that other more sophisticated metrics may provide greater

taken for this study to allow fast generation of the metrics studied.

correlation to the motility seen in the AC; however a simplistic approach was

In conclusion the line analysis index of colonic motility derived from cine MRI

registered data provides a quick, accurate and non-invasive method to detect

wall motion within the ascending colon following a colonic stimulus in the form of

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approach not available with this data, which was looked at retrospectively. It is

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a macrogol drink.

Health.

Abbreviations:

AC – Ascending colon

Acknowledgements, funding and disclosures

conflicts of interest to disclose.

bTFE – balanced Turbo Field Echo

- HV – Healthy volunteers
 - LA Line analysis
 - MRI Magnetic Resonance Imaging
 - NAC Normalised Area Change
 - PEG - polyethylene glycol
- ROI – Region of Interest
- .ation of Intensity SD_JAC – Standard deviation of the Jacobian
- SD_I Standard deviation of Intensity

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- Tables
- Table 1. Demographics of the two subject groups, data presented as mean (std dev)

	Total Cohort	Inter-observer		
	(N=23)	Group (N=11)		
Gender M / F	11/12	3/8		
Mean Age (yrs)	27.1 (8.5)	26.7 (10.2)		
Age Range (yrs)	19-50	20-50		
BMI (kgm ⁻²)	23.2 (2.4)	23.2 (2.3)		

1 Table 2. Correlation of potential metrics with the observer rating score.

		- 55	
Metric	Spearman Rho	95% Confidence	p-value
	correlation	interval of coefficient	•
SD_JAC	0.492	0.199-0.704	0.002
SD_I	0.368	0.050-0.619	0.021
LA _{0.25mms-1} Index	0.673	0.447-0.819	<0.001
LA _{0.5mms-1} Index	0.739	0.545-0.858	<0.001
LA _{0.75mms-1} Index	0.649	0.411-0.804	<0.001
NAC _{3%} Index	0.366	0.047-0.617	0.022
NAC _{5%} Index	0.353	0.032-0.608	0.028
NAC10% Index	0.329	0.006-0.590	0.041

Table 3. Bland-Altman Limits of Agreement and Intra class correlation

coefficients for intra- and inter-observer measurements of the LA metrics

(N=33).

Metric (range of	Intra-observer			Inter-observer		
observation 1)	Bias	95% Limits of	ICC	Bias	95% Limits of	ICC
		Agreement			Agreement	
LA _{0.25mms-1} Index	0.014	-0.046-0.074	0.981	-	-0.096-0.085	0.956
(0.009-0.625)			*	0.005		*
LA _{0. 5mms-1} Index (0.000-0.353)	0.007	-0.039-0.052	0.964 *	0.001	-0.051-0.054	0.947 *
* p<0.001						1

* p<0.001

1 Figure Legends

Figure 1. Sagittal images through the AC showing; (A) Placement of lines for line
analysis (LA) index (B) Position of ROIs for normalised area change (NAC) index

Figure 2. (A) Example images from cine MRI data showing overlay (red/blue) of
standard deviation of Jacobian. Original data as insert. (B) Example single
smoothed line length plot from mid AC. (C) Wall displacement motility plots from
line analysis, colour bar indicates change in length of smoothed line length from
mean. (D) Wall velocity motility plot, colour bar indicates change in consecutive
line lengths after smoothing.

Figure 3. Graphs showing correlation between motility metrics and observer
rating scores for non-baseline data. (A) SD_JAC, (B) SD_I, (C) LA_{0.5 mms⁻¹} motility
index, (D) NAC_{5%} motility index.

Figure 4. Examples of different types of colonic motility shown on line analysis plots of displacement and velocity. (A) 3 retrograde segmental contractions – black arrow heads. (B) 2 whole AC retrograde contractions – grey arrow. (C) Near simultaneous high amplitude whole AC contraction – black arrow. (D) Low amplitude retrograde contraction – Grey arrow heads. Red regions on the displacement maps represent an large increase in the lumen diameter compared to the mean value. This is highlighted by the white arrow heads on B and C. Figure 5. Box and whisker plot showing the variation of LA_{0.5mms⁻¹} with both time

26 and macrogol stimulus. Groups N=11 1L drink, N=12 2L drink. Missing data

1		
2 3 4	1	due to breathing artefacts baseline: N=2 1L, N=2 2L; T=0 mins: N=2 1L, N=3
5	2	2L; T=60 mins: N=1 1L, N=1 2L.
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