Original Article

MRI tagging of colonic chyme mixing in healthy subjects: Inter-observer variability and reliability of the measurement with time

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Abstract:

Background: MRI tagging techniques have been applied to the GI tract to assess bowel contractions and content mixing. We aimed to evaluate the dependence of a tagging measurement (for assessing chyme mixing) on inter-observer variability in both the ascending colon (AC) and descending colon (DC) and to investigate the temporal variation and hence reliability of the colonic tagging technique by acquiring multiple measurements over time on healthy participants.

Methods: Two independent datasets of healthy adults were used for the retrospective inter-observer variability (Study 1: 13 datasets and Study 2: 31 datasets) and ten participants were scanned for the prospective temporal variation study following a 1L mannitol oral preparation. All colonic tagging data were acquired on 3T MRI scanners. The mean and the standard deviation (std dev) maps were generated pixel-by-pixel using custom-written software in MATLAB. The colonic regions of interest were defined using MIPAV software. Bland-Altman plots and scatter plots were used for the inter-observer variability. The mean and std dev of all repeated measures for each subject were calculated along with a one-way ANOVA to test for variations with time.

Results: Scatter plots and Bland-Altman plots showed a large range of data with low variation and small limits of agreements (<5% CoV). The intraclass correlation coefficient of inter-rater reliability was excellent and 0.97 or above for the AC and DC measurements for both datasets. The temporal variation study shows that there was no significant difference found between the multiple measures with time ($P = 0.53$, one-way repeated measures ANOVA test).

Conclusions: MRI tagging technique can provide an assessment of colonic chyme mixing. The inter-observer study data showed high inter-rater agreement. The temporal variation study showed some individual variations with time suggesting multiple measurements may be needed to increase accuracy.

Keywords: bowel motility, colonic tagging, colonic chyme, magnetic resonance imaging, IBD.

Key Points:

- MRI tagging can be used to quantify colonic chyme mixing; the inter-rater agreement between the measurements of the technique carried out by two different trained observers was found to be excellent.

- Multiple scans of the MRI tagging technique are required to increase the assessment accuracy of the colonic chyme mixing, this was suggested after performing the technique on healthy subjects following a 1L mannitol drink.

- MRI tagging technique could be used to provide objective measures for the colonic motility assessment in both inflammatory and functional bowel diseases.

1. Background

Inflammatory bowel diseases (IBDs) are chronic conditions that cause bowel damage and disability.[1,2] Recently, cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have become increasingly popular for assessing IBD. CT can detect the bowel complications and extension of IBD, but its use is restricted by radiation exposure.[3] Non-invasive colonic imaging using MRI, which does not use ionizing radiation, may have a role in quantifying different aspects of colonic disease activity and bowel motility as well. MRI can be an effective diagnostic tool for detecting colonic inflammation in patients with IBD particularly when a colonoscopy is incomplete or not possible.[4]

In addition, MRI can provide an indication of the motility and physiology of the bowel using cine sequences.[5] Changes in motility and bowel function might predate structural changes in intestinal inflammation, which for the most part inhibits motility.[6] Menys *et al*.[7] assessed bowel motility using MRI and found that small bowel motility in chronic intestinal pseudo-obstruction (CIPO) patients were lower compared to the healthy controls. The bowel wall motility will directly affect the movement of the chyme through the intestines; however, chyme mixing is not a direct measurement of the wall motility but is a marker of the fluidity of the content, the colonic wall motility and the pressures within the colonic segments. Motility measures in the colon might have other uses in functional diseases as well as drug distribution testing in colonic release formulations.

To provide quantitative measurement of both small bowel and colonic motility, MRI tagging techniques are being rapidly developed and have been applied to the gastrointestinal (GI) tract. MRI tagging was initially developed to assess cardiac function by using a

magnetisation grid to trace and evaluate tissue distortion and myocardial contraction.[8] MRI tagging has been assessed in previous studies to quantify bowel contractions[9] and colonic chyme mixing.[10] The method described by Pritchard *et al*.[10] assessed the colonic chyme mixing by observing the signal intensity changes through time measured from a tagged cine MRI acquisition and showed significant differences between healthy and constipated subjects, following a strong laxative drink. Measuring chyme mixing would be clinically useful in conditions where colonic motion is linked to patient symptoms like IBDs, as the measurements are objective (unlike subjective symptom reporting) and may reflect changes to inflammation levels due to 'flare ups' or from treatment response.

This study aims to provide additional investigations for the tagging technique by (i) evaluating the inter-observer variability of the analysis measurement in both the ascending colon (AC) and descending colon (DC); (ii) defining the short-term temporal variation of the measurements following a 1L oral preparation drink which is commonly used for magnetic resonance enterography (MRE) studies in IBD, instead of the strong laxative oral drink which has been used in previous studies of the technique. These measurements will then inform future protocols to assess colonic chyme mixing in prospective cohort studies of IBD patients.

2. Materials and Methods

2.1. Study design/subjects

Inter-observer variability study:

The inter-observer variability assessment was a retrospective study using two independent datasets of healthy adults. Study 1: the data came from 13 datasets from 10 subjects following a 1L mannitol drink (unpublished data). Study 2: the data came from Wilkinson-Smith *et al*.[11]: following a 0.5-1L Moviprep® drink including 31 datasets from 8

subjects. All studies were approved by the local Research Ethics Committees (J/3/2007/14 for Study 1; UoN FMHS D10052016 for Study 2).

Temporal variation study:

Healthy participants (without any history of GI disease or use of medication known to affect GI transit) were scanned prospectively. Participants arrived at the test centre fasted and were given 1L of oral bowel preparation (2.5% mannitol with 0.2% locust bean gum), to ingest slowly over 40 minutes. The scanning session was performed two hours after participants started consuming the oral contrast to allow the contrast to move into the colon (t=120 minutes). The study was approved by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (146-1811-04), and written informed consent was obtained from all participants involved in the study.

2.2. MRI protocol and tagging acquisition

Colonic tagging data were acquired on a 3T Ingenia wide-bore and a 3T Achieva MRI scanner (Philips, Best, The Netherlands) for the inter-observer variability study and temporal variation study, respectively, which are similar in performance. In all studies, participants were positioned supine in the MRI scanner with an abdominal parallel imaging receiver coil wrapped around the abdomen (DS anterior coil for Ingenia and a 16-channel XL Torso coil for Achieva). The tagging scan was a 20-second cine breath-hold balanced turbo field echo (bTFE) sequence, with a single sagittal oblique slice (2D) placed through the AC (or DC – inter-observer study only) with 33 frames were acquired at 600 ms intervals, SENSE factor 1.5, and half-scan factor 0.7, dark horizontal strips (tag lines) which were 12 mm apart (field of view = 330 x 259 mm^2; reconstructed resolution = 0.98 x 0.98 mm^2; flip angle = 45°; slice thickness = 15 mm).

In the temporal variation study, the MRI tagging scans were positioned to cover the central AC or DC in separate 10 min time window acquisitions with 10 independent repeated measurements over time, with scans acquired at approximately 1-minute intervals. However, due to a lack of oral contrast reaching the DCs, only a few images were taken for the DC regions, as the contrast was too poor between the tag lines and content, therefore, the DC data were excluded. The comparison between the two studies is illustrated in Table 1.

2.3. Image analysis

The analyses were performed in a similar way for both the inter-observer assessment and the temporal variation study. The mean and the standard deviation (std dev) maps of the AC (Figure 1) or DC were generated pixel-by-pixel using custom-written software[10] in MATLAB® (The MathWorks Inc). The colonic regions of interest (ROIs) were then delineated by the observers (MA with one year experience, while AA and VWS with three years' experience) using MIPAV software[12] using the mean map as the reference image to draw on and delineate the edges of the region, and the resulting coefficient of variation (%CoV) was calculated and defined as:

$$\text{CoV\%} = \text{ROI pixel std dev map} * 100\% / \text{ROI pixel mean intensity map}$$

Mixing of colonic chyme results in movement and smearing of the tag lines results in larger std dev values increasing the %CoV. For the inter-observer variability study: two observers for each study independently defined the ROIs. The two different studies used different observers to look at the data so the studies could not be combined. For each tagging scan on the temporal variation study, a different (individual) ROI around the colon region was drawn and %CoV was measured, this avoided shifts in the colonic position altering the ROI to include tissue outside the colon region under investigation. For the 10 repeated %CoV

calculated for each participant, a mean and std dev of all repeated measures was calculated along with the mean and std dev for the first 5 repeated measurements and last 5 repeated measurements separately.

2.4. Statistics:

Statistical analysis for both studies was performed using SPSS (IBM SPSS Statistics, v27; IBM Corp) and GraphPad Prism Version 9.0.0 (GraphPad Software, San Diego, CA, USA).

Inter-observer variability study:

Inter-rater reliability analysis was estimated with a 2-way mixed-model, absolute agreement intraclass correlation coefficient (ICC) with a 95% confidence level. Interpretation of ICC inter-rater agreement measures was rated following the Koo, T. K et al. guidelines[13]: below 0.50: poor, between 0.50 and 0.75: moderate, between 0.75 and 0.90: good, above 0.90: excellent. Bland-Altman plots and scatter plots with the identity line were also used to visualize the inter-observer variability assessment data.

Temporal variation study:

The Pearson Correlation coefficient of the mean versus the std dev of the 10 repeated measurements was calculated to determine whether there was an increase in the variability of the multiple measurements of the colonic tagging with increased %CoV (increased mixing). It would be useful clinically to reduce the number of measurements of tagging across the data if variability was detected, therefore, the mean and std dev for the first five and last five repeated measurements was calculated and compared to the full 10 repeated measures. A one-way repeated measure ANOVA analysis was conducted to investigate whether there was any trend in the data acquisition with time.

3. Results

Inter-observer variability study:

Scatter plots (Figure 2) and Bland-Altman plots (Figure 3) showed a low variation and small limits of agreements (<5% CoV). Table 2 shows a bias and 95% limits of agreement in the Bland-Altman analysis and the observer 1 data. The ICC of inter-rater reliability of Study 1 (N=13) was excellent; 0.97 (95% CI, 0.93-0.99) for the AC measurements, 0.98 (95% CI, 0.92-0.99) for the DC measurements. The ICC of inter-rater reliability of Study 2 (N=31) was excellent; 0.97 (95% CI, 0.94-0.98) and 0.98 (95% CI, 0.96-0.99) for the AC measurements and the DC measurements, respectively. Table S1 (Supplementary Materials) shows the %CoV of the full AC and DC measurements for Study 1 and Study 2 colonic tagging datasets of all observers.

Temporal variation study:

Ten participants were recruited: five females and five males, mean age of 29 years old (std dev 10). The change over time between the multiple measurements, for all participants, due to variations in colonic chyme mixing is shown in Figure 4 showing that the measurement is quite variable over time. To compare the time variation between the different measures, mean data were calculated for all 10 repeated scans, then the first five, and last five scans, respectively. The mean data of the calculated %COV for the first five and last five scans are shown in Figure 5. These data didn't show any obvious consistent time variation between the different measures. The mean and std dev of the calculated %COV for each subject are shown in Table S2 (Supplementary Materials). The correlation between the mean and std dev of the ten scans is shown in Figure 6. The direction of the relationship is positive, meaning that these variables tend to increase together slightly with increased colonic chyme mixing (Pearson r=.392, P = 0.263 for a two-tailed test).

There was no significant difference found between the multiple measures with time within participants (P = 0.53, one-way repeated measures ANOVA test). The correlation between the mean and std dev of the first 5 and last 5 scans separately are shown in Figure S1 (Supplementary Materials).

4. Discussion

MRI tagging can be used to quantify and assess colonic chyme mixing. Chyme mixing is generally a result of colonic wall motility when fluid is present in the colon. However, it can be visualized for a time period beyond the end of the wall motion and may occur at a distance from the wall motion due to pressure changes. This makes shorter measurement periods possible when compared to directly observing the wall motion and this makes the technique more clinically applicable than direct wall motion observations which generally need several minutes of data acquisition. In this study, the approach using the CoV analysis method provided excellent agreement between the measurements carried out by two different trained observers. There was little difference between both AC and DC measurements of the colonic tagging CoV with a high inter-rater agreement. These results add further validation data to previous research [11], of colonic chyme mixing as a potential imaging marker, which demonstrated the test-retest accuracy of the MR tagging technique to assess the colonic chyme mixing before and after a strong laxative challenge drink. We were able to show that even without such a powerful stimulus, tagging allows a reproducible assessment of colonic chyme mixing suggesting it could be useful in assessing the lesser responses seen after feeding and other such physiological stimuli. This non-invasive technique could be used to provide objective measures for the motility assessment of the colon in both inflammatory and functional bowel diseases.

The results of this small-scale temporal variation study indicate that the time of acquisition following ingestion did not influence the measurement of colonic chyme mixing, however, the individual values measured, showed some variability over the 10-minute acquisition window which indicates that a single assessment of tagging might not be a good biomarker as data would be quite variable. These results which were measured after consuming the mannitol drink are mostly within the range of the mean values presented by a previous study of Wilkinson-Smith *et al*.[11] which were calculated after consuming a strong laxative drink. This indicates the outcomes of the colonic chyme mixing assessment of our study are consistent with the Wilkinson-Smith study and would also suggest similar colonic wall motility to the Wilkinson-Smith study driving the chyme mixing, however no wall motion was assessed here. Nevertheless, the results of our study suggest that multiple measurements may be needed to accurately assess this parameter following the mannitol oral contrast drink. Averaging the measurements gives an overall singular value for the mixing (making comparisons easier and reducing biomarker variability). Averaging the measurements would smooth out any meaningful physiological differences in chyme mixing across time, however these could be assessed by calculating the standard deviation of the mean. 9 out of 10 subjects had their mean 'first 5' and 'last 5' CoV measurements within one std dev of the whole dataset mean which indicates that 5 scans could be sufficient to characterize reliably the colonic chyme mixing precisely and would reduce scan time. Within-subject measurements of all ten colonic tagging scans show a slight trend for increased std dev with increasing mean %CoV which indicates that the variation increases slightly with increased colonic chyme mixing. Multiple measurements of this non-invasive technique can be used in future studies that aim to look at bowel motility and treatment response of IBD patients, using the same water-based laxative to avoid having any additional abdominal pain,

rather than using a strong stimulus such as Moviprep® which was used previously in the constipation studies.[10,14]

The main limitation of this study was the relatively small number of subjects included for the inter-observer variability assessment and the temporal variation study. Also, the DC data from the temporal variation study were excluded due to a lack of oral contrast in this segment which did not allow us to take all the planned images. In addition, the type of laxative used in the temporal variation study is different than the oral contrast drink used in the Wilkinson-Smith study *et al*.[11] which means these results may only apply to the type of laxative we used here with the same timings. However, the drink will be better tolerated in the IBD cohort.

5. Conclusions

The MRI tagging technique of percentage coefficient of variation showed high inter-rater agreement between two different observers across two independent datasets. Scans of MRI tagging of the ascending colon, following a water-based laxative drink, showed some variability suggesting multiple scans are required for an accurate assessment of the colonic chyme mixing. Future work should investigate and confirm the reliability of acquiring this technique in larger cohorts of both healthy participants and patients and the variability of responses to other stimuli including test meals and drinks.

Author Contributions: methodology, M.A., L.M., G.W.M., and C.L.H.; software, C.L.H.; formal analysis, M.A., C.L.H.; investigation, M.A., L.M., G.W.M., and C.L.H.; writing—original draft preparation, M.A., L.M., G.W.M., and C.L.H.; writing—review and editing, all authors. All the authors read and approved the final manuscript.

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Institutional Review Board Statement: the study was approved by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (146-1811-04).

Informed Consent Statement: informed consent was obtained from all subjects involved in the study.

Data Availability Statement: datasets are available upon request.

Conflicts of Interest: GWM has received educational support from Abbvie, Janssen, NAPP, Takeda Pharmaceuticals, Merck Sharp & Dohme Ltd, Ferring and Dr Falk. He has received speaker honoraria from Merck Sharp & Dohme Ltd, Abbvie, Janssen, Ferring and Takeda Pharmaceuticals. He attended advisory boards for Abbvie, Celgene, Takeda Pharmaceuticals, Janssen, Medtronic, Phebra Pharmaceuticals, Servertus Associates Ltd and Dr Falk. Dr Moran is a consultant for Alimentiv. RCS has received speaker's fees from Ardelyx, F.Trenka and Bi Pharma Consultants and research funding from Sanofi-Aventis Deutschland GmbH.

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Tables:

TABLE 1: A comparison between the two studies.

Study name	Inter-observer variability study	Temporal variation study
Study type	Retrospective	Prospective
MRI Scanner type	3T Ingenia	3T Achieva
Contrast type	1L mannitol drink (for study 1) 0.5-1L Moviprep® drink (for study 2)	1L mannitol drink (2.5% mannitol with 0.2% locust bean gum)
Time points (measurements)	60 minutes and 120 minutes	120 minutes
Colonic segments	AC and DC	AC (DC excluded for poor contrast)
Scan time	1 min to cover AC and DC in two breath holds (AC – 1 Breath hold, and DC – 1 breath hold)	10 min (1 acquisition per minute each acquisition in a single breath hold)

TABLE 2: Bias and 95% limits of agreement in Bland-Altman analysis for Study 1 and Study 2, and the observer 1 data.

Colonic tagging datasets	Bias	95% Limits of Agreement (lower)	95% Limits of Agreement (upper)	Observer 1			
				Average	Std Dev	Range	
						min	max
Study 1 (AC)	-0.56	-3.44	2.32	20.5	7.5	8.5	31.7
Study 1 (DC)	0.84	-1.99	3.68	19	8.3	9.2	40.3
Study 2 (AC)	0.00	-3.84	3.83	25.3	8.1	13	50.7
Study 2 (DC)	0.20	-2.67	3.06	24.3	8.9	10.9	46.2

AC, ascending colon; DC, descending colon; Std Dev, standard deviation.

Figure legends:

FIGURE 1: The generated maps of the ascending colon after applying the tagging (dark horizontal stripes across the image), (i) Pixel mean intensity map, (ii) Corresponding pixel standard deviation (std dev) map, and (iii) high resolution T2 image (sagittal oblique) with anatomical labels. A visible small motion of colonic chyme is highlighted (white arrow) which is indicated by the tags distortion. Colon regions (ROIs) are outlined in red.

FIGURE 2: Scatter plot for Study 1(top) and Study 2 (bottom) colonic tagging datasets, with identity line.

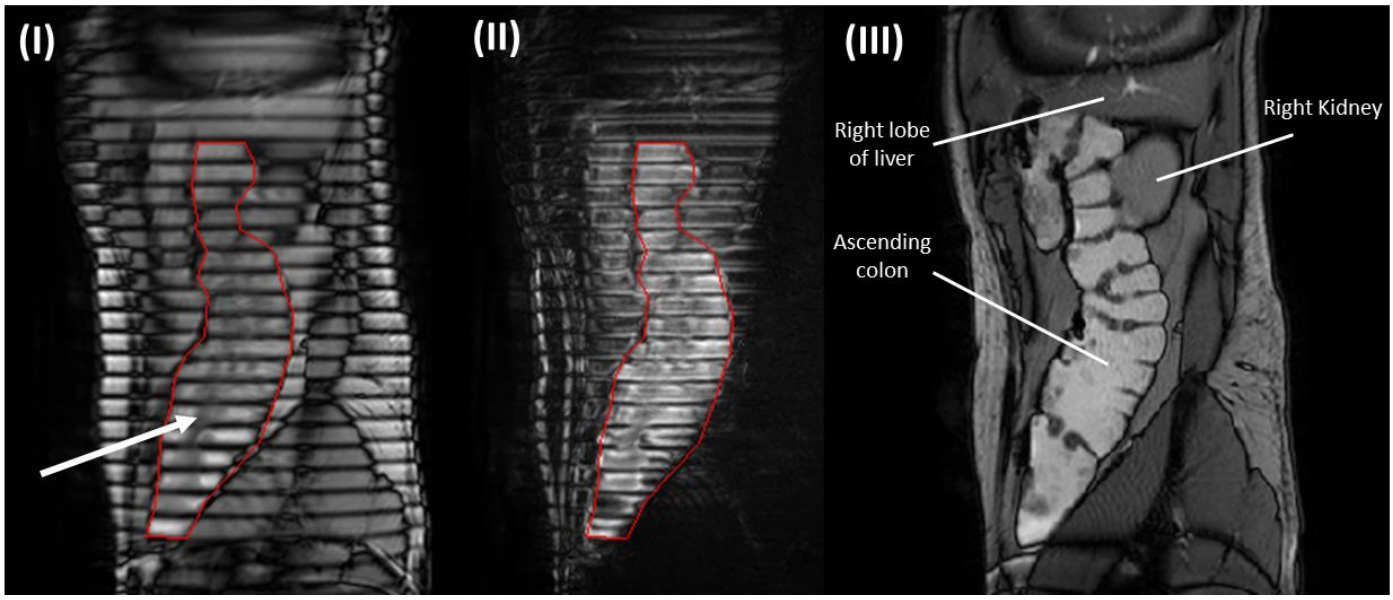
FIGURE 3: Bland-Altman plots for Study 1 and Study 2 colonic tagging datasets which describe agreement between the measurements separately for ACs and DCs. They show difference vs average with dotted lines representing bias and 95% limits of agreement.

FIGURE 4: The change over time between the temporal scans for the ascending colon (AC). The scan was acquired approximately every minute over 10-minute period.

FIGURE 5: The mean data of the calculated %COV for the temporal first five and the last five scans.

FIGURE 6: Mean and standard deviation (std dev) of coefficient of variation (%COV) for each subject (within subject) of all the temporal scans.

Figures:



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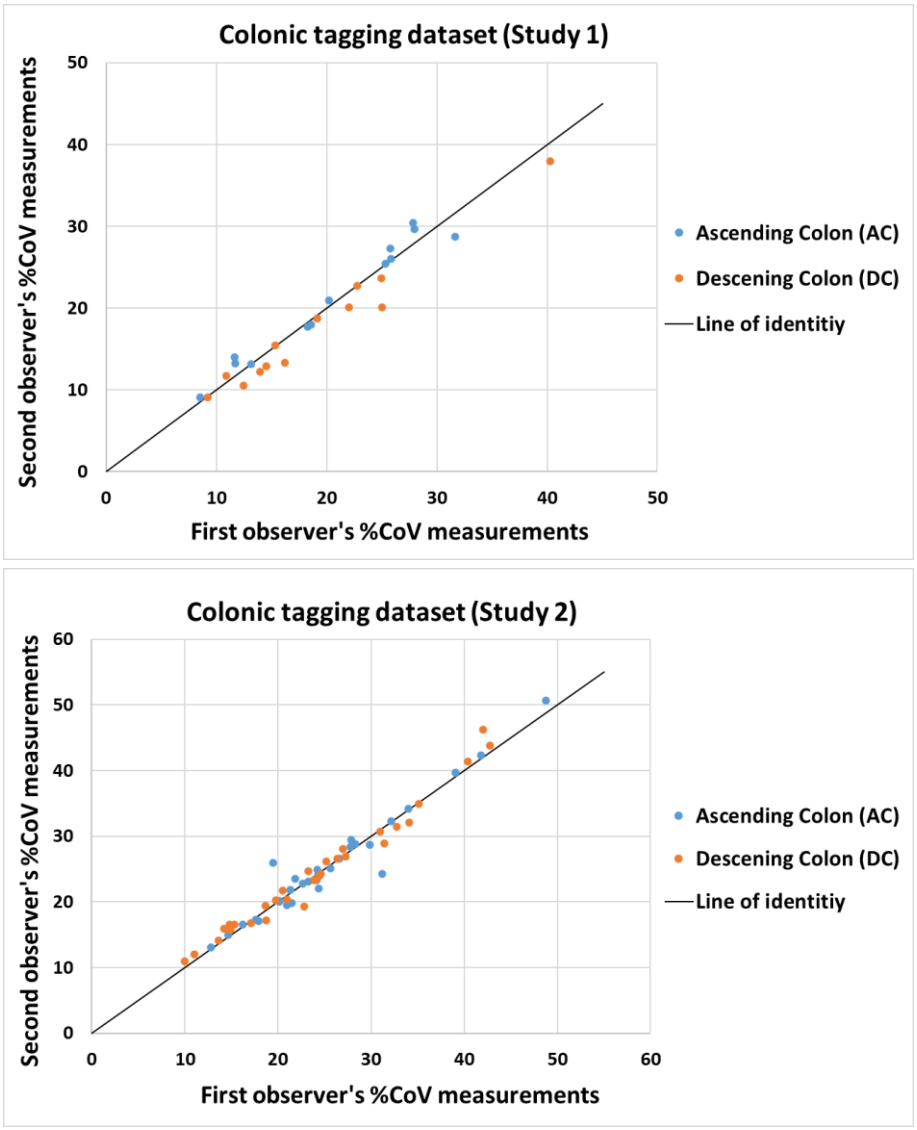
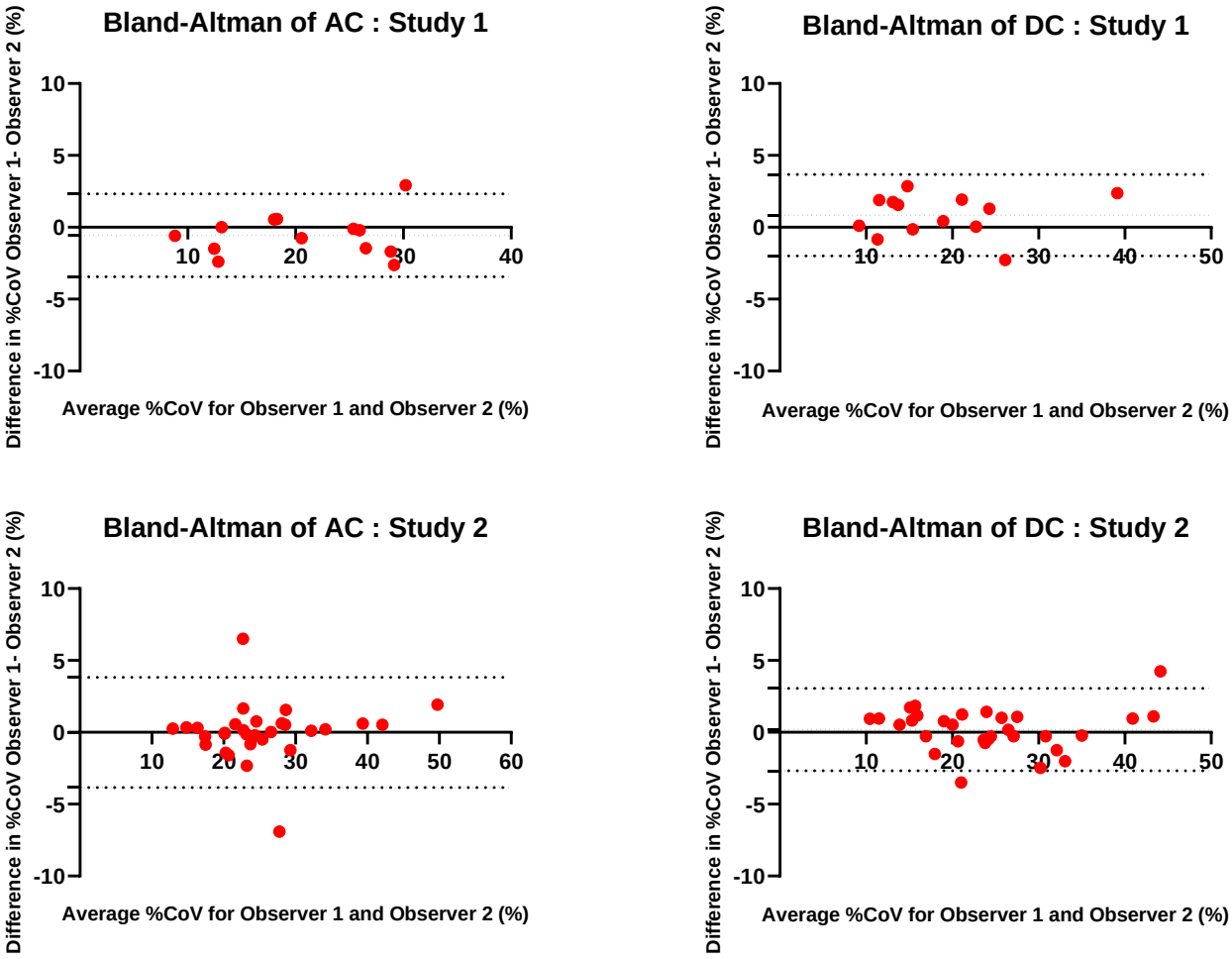


FIGURE 2: Scatter plot for Study 1(top) and Study 2 (bottom) colonic tagging datasets, with identity line.



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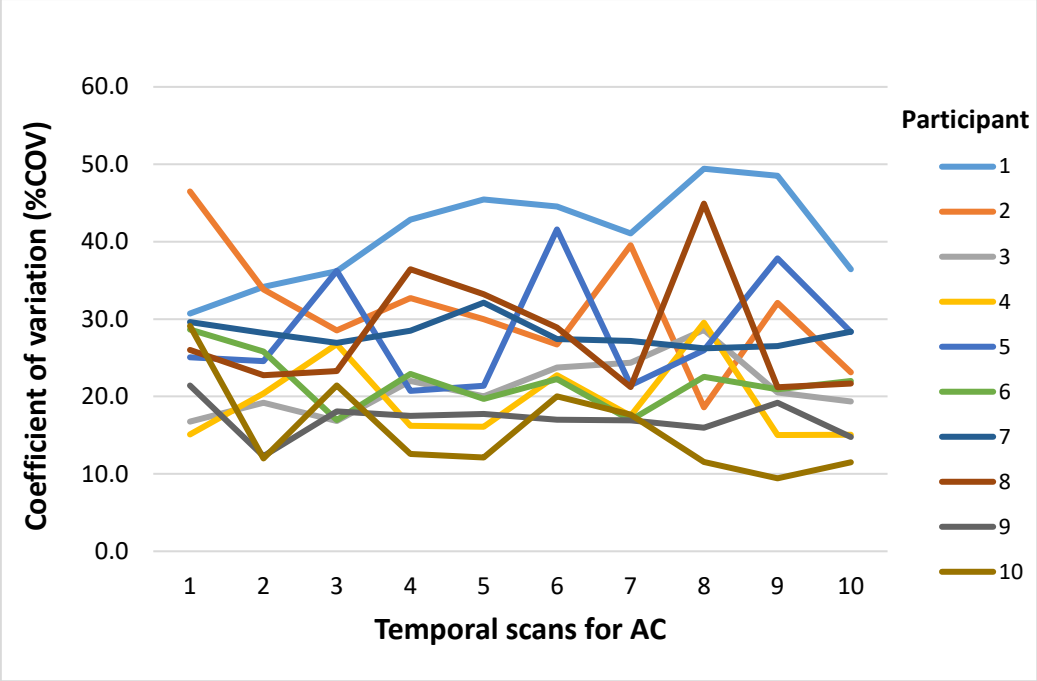

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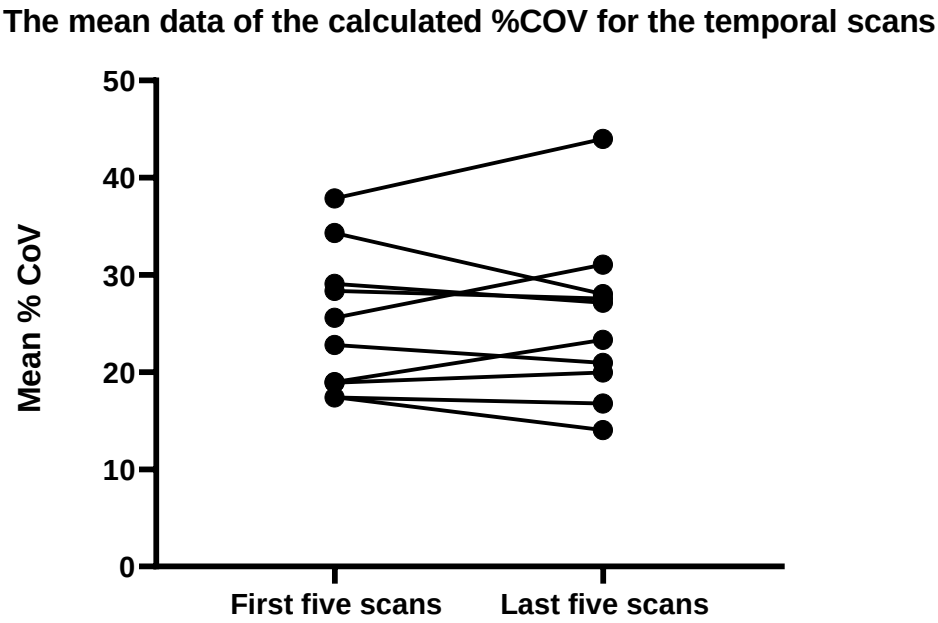

FIGURE 5: The mean data of the calculated %COV for the temporal first five and the last five scans.

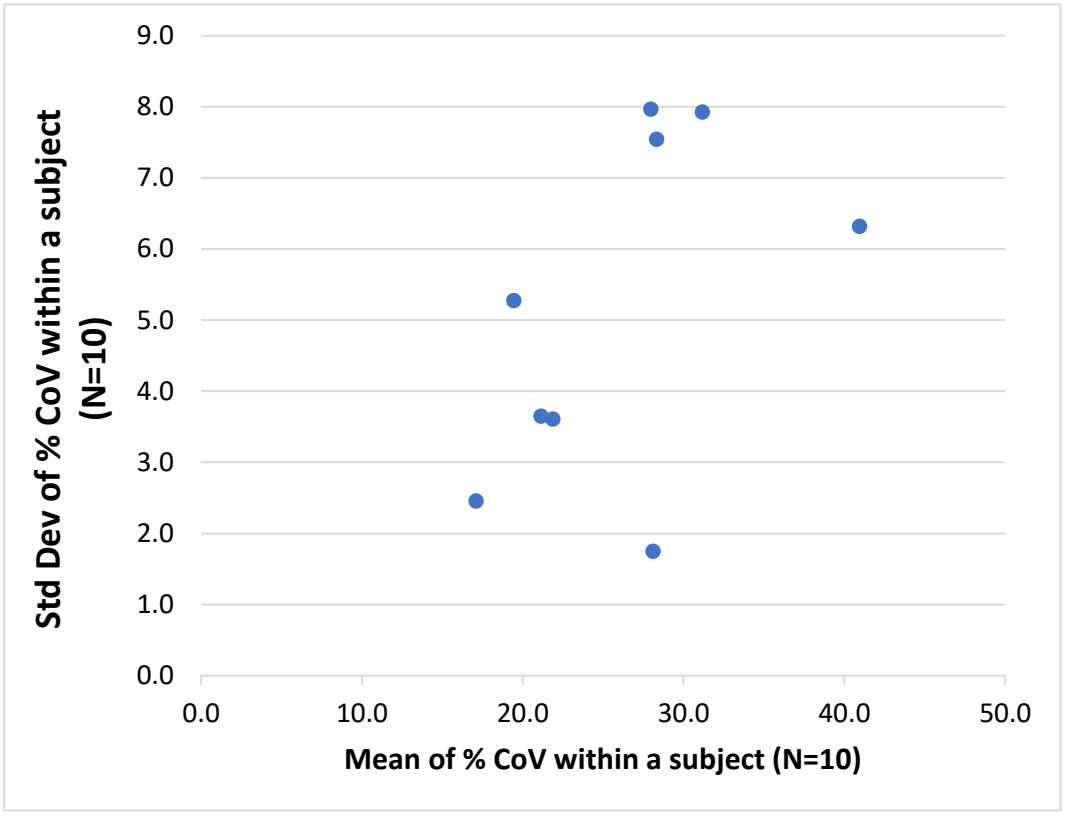

FIGURE 6: Mean and standard deviation (std dev) of coefficient of variation (%COV) for each subject (within subject) of all the temporal scans.