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Comparison of gastrointestinal landmarks using the gas-sensing capsule and wireless motility capsule

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Summary

Background: Accurate definition of the gastroduodenal and ileocaecal junctions (GDJ, ICJ) is essential for the measurement of regional transit times.

Aims: To compare the assessment of these landmarks using the novel gas-sensing capsule and validated wireless motility capsule (WMC), and to evaluate intra-subject variance in transit times

Methods: Healthy subjects ingested the gas-sensing capsule and WMC tandemly in random order. Inter-observer agreement was evaluated by intra-class correlation coefficient (ICC). Agreement between the paired devices' transit times was assessed using Bland–Altman analysis; coefficient of variation was performed to express intra-individual variance in transit times. Similar analyses were completed with tandemly ingested gas-sensing capsules.

Results: The inter-observer agreement for landmarks for both capsules was excellent (mean ICC ≥0.97) in 50 studies. The GDJ was identifiable in 92% of the gas-sensing capsule studies versus 82% of the WMC studies ($p = 0.27$); the ICJ in 96% versus 84%, respectively ($p = 0.11$). In the primary cohort ($n = 26$), median regional transit times differed by less than 6 min between paired capsules. Bland–Altman revealed a bias of −0.12 (95% limits of agreement, −0.94 to 0.70) hours for GDJ and − 0.446 (−2.86 to 2.0) hours for ICJ. Similar results were found in a demographically distinct validation cohort ($n = 24$). For tandemly ingested gas-sensing capsules, coefficients of variation of transit times were 11%–35%, which were similar to variance between the paired gas-sensing capsule and WMC, as were the biases. The capsules were well tolerated.

Conclusions: Key anatomical landmarks are accurately identified with the gas-sensing capsule in healthy individuals. Intra-individual differences in transit times between capsules are probably due to physiological factors. Studies in populations with gastrointestinal diseases are now required.

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1 | INTRODUCTION

Assessment of intestinal transit can assist with diagnosing suspected dysmotility and subtyping disorders of gut-brain interaction by distinguishing abnormal regional and global gastrointestinal transit. It also has the potential to help guide the assessment of response to therapy and to identify those patients with multiregional dysmotility, who are not easily distinguished clinically.[1,2] Currently, regional transit may be assessed using conventional methods, such as scintigraphy and radio-opaque marker studies,[3–5] both of which are limited by lack of standardisation and radiation exposure. The wireless motility capsule (WMC) was approved by the Food and Drug Administration in 2006 and has been validated against these reference standard tests for use in gastroparesis and chronic idiopathic constipation.[6,7] It has the benefits of providing global as well as regional transit assessments in ambulatory patients in the absence of radiation and, therefore, enables it to be repeated without risk of cumulative radiation exposure. However, the pH sensor of the WMC has limited sensitivity and a naturally low signal-to-noise ratio because it is a Nernst-type sensor. Thus relatively small voltages are produced for pH changes, which are susceptible to external influences, such as environmental electromagnetic fields (for example, present around an electrical cord).[8,9] These features may interfere with the detection and accuracy of the signals, and can contribute to failure to recognise important landmarks enabling regional transit assessment, specifically gastroduodenal and/or ileocaecal transit, in up to 15% of patients.[6,7,10–13]

A novel, ingestible telemetric gas-sensing capsule measures different analytes in comparison to those measured by WMC. These include the capability of measuring concentrations of hydrogen and carbon dioxide gas species and anaerobicity of the environment, which might offer, for example, unique insights into the regional fermentative activity of the gastrointestinal lumen.[14] The potential advantages include higher signal-to-noise ratios by virtue of the chosen gas sensors being resistive-type, and therefore more resistant to the influence of environmental factors seen with the Nernst-type sensors.[8] However, accurately identifying the capsule's regional location within the gastrointestinal tract (stomach, small intestine, large intestine) is essential to enable the interpretation of such information. Pilot studies using an earlier capsule model in both pig and human gastrointestinal tracts have demonstrated technical reliability and safety, and have suggested accuracy in the detection of the key anatomical landmarks (specifically, gastroduodenal and ileocaecal junctions [ICJs]).[15–19] However, the methodology used to identify these key landmarks requires validation.

The current study aimed to determine the interobserver agreement in defining these key landmarks and to compare regional and whole gut transit time (WGTT) measurements obtained by the gas-sensing capsule with those from the WMC in tandem ingestion experiments in healthy adult humans. To enhance interpretation, the variance in the assessment of landmarks and thus transit times in the individual was determined by tandem ingestion of two gas-sensing capsules.

2 | MATERIALS AND METHODS

2.1 | Subjects

Healthy volunteers without known gastrointestinal disease and aged 18–65 years were invited to participate in this pilot study (referred to as the 'primary cohort'). A separate cohort of healthy volunteers from a second site (in New Zealand) was recruited to participate as the 'validation cohort'. Subjects were screened by clinical investigators prior to enrolment. Exclusion criteria were similar to previous capsule studies[6,7,20] and specific to the current study requirements. Specifically, subjects were excluded if they had regular gastrointestinal symptoms suggestive of a disorder of gut–brain interaction; known structural gastrointestinal disease; difficulty swallowing; previous abdominal surgery, history of radiation enteritis, gastric bezoar or bowel obstruction; the presence of a medical condition that may alter gastrointestinal motility (including endocrine and neurological); an implantable device such as a pacemaker; use of antibiotic, prebiotic or probiotic in the past 4 weeks; use of proton pump inhibitor or H_2 receptor antagonist in the past 7 days; prokinetic use in the preceding 48 h; body mass index (BMI) >35 kg/m^2 (Australian cohort) or > 27 kg/m^2 (New Zealand cohort) or current pregnancy or breastfeeding.

2.2 | Protocol

The protocol was approved by the Monash University Human Research Ethics Committee and the Northern B Health and Disability Ethics Committee prior to commencement of the study and was registered on the Australian New Zealand Clinical Trials Registry (registration number ACTRN12619001219178).

After an overnight fast of at least 8 h, participants consumed a 1092 kJ nutrient bar (SmartBar, Medtronic) with a glass of water followed by tandem ingestion of two capsules that had been activated and calibrated according to the manufacturer's instructions. For the primary and validation cohorts, one gas-sensing capsule and one WMC were ingested in tandem. The order of ingestion was randomised in blocks of 20 (www.randomization.com). Following capsule ingestion, the participants then fasted for a further 6 h prior to resuming their usual diet but were permitted to consume at least 50 ml of ambient temperature water every 30 min for the first 2 h of the study. Strenuous activity and smoking were discouraged. Participants were instructed to wear a bag containing both data receivers on their body for the duration of the study (keeping the receivers within 1.5 m), and to record bowel movements and any symptoms. When capsule excretion could not be confirmed using its signal, plain abdominal imaging was performed. This same protocol was followed for both the primary and validation cohorts. In the tandem gas-sensing capsule study cohort, two activated gas-sensing capsules were ingested under the same conditions.

2.3 | The WMC monitoring system

The SmartPill® WMC monitoring system (Medtronic) consists of a single-use, non-digestible capsule (26 mm × 13 mm), which transmits data related to pH (range 1–9.0 pH units), temperature (25–49°C) and pressure (0–350 mmHg) via a frequency of 434 MHz to a wearable data receiver from which results can be downloaded and interpreted using dedicated software (MotiliGI, version 3.0, Medtronic).[21]

Using this system, anatomical landmarks are identified by changes in temperature and pH profiles along the gastrointestinal tract (Table 1).[1,6,21–23] Briefly, *ingestion* is defined as an increase in temperature (ambient to body temperature) and represents $t = 0$. *Excretion* is defined as either a loss of signal or drop in temperature corresponding to a bowel motion. The gastroduodenal junction (GDJ) is identified by a sharp rise in pH (more than three units) from gastric baseline or to a pH of greater than 4 pH units, corresponding to the passage of the capsule from the acidic gastric environment to the more basic duodenal environment. The *ICJ* is identified by a fall of ≥1 pH unit distal to gastric emptying lasting for at least 10 min. Transit times are calculated as the time between capsule ingestion and entry into the duodenum through the GDJ for gastric emptying time (GET), GDJ and ICJ for small bowel transit time (SBTT), ICJ and excretion for colonic transit time (CTT), and ingestion and excretion for WGTT. GETs greater than 6 h were excluded.[6]

Data were evaluated using the dedicated software and visually derived transit times were calculated blindly by two trained investigators (P.A.T., C.K.Y.). In the instance of disagreement (>10% difference), a third experienced assessor (R.E.B.) provided an additional opinion. The transit times recorded for analysis were an average of the two investigator transit reports (or the adjudicator report).

2.4 | Gas-sensing capsule system

The gas-sensing capsule system (Atmo Biosciences) consists of a single-use, non-digestible capsule (28 mm × 11 mm), data receiver, smart phone with application and secure cloud storage. Studies with two earlier capsule versions, which had fewer features and utilised different measures for the landmarks, demonstrated inferior performance in the assessment of the landmarks, as described in Figure SS1. All subsequent studies were performed with the latest capsule version 2.1, which has additional features and more comprehensive landmark assessment (Table 1). Specifically, the latest device evaluates concentrations of total relative volatile organic compounds, hydrogen, carbon dioxide, temperature, capsule orientation and changes in the physical electromagnetic properties of the environment surrounding the capsule. Measurements are transmitted from the capsule at a frequency of 434 MHz to a patient-worn data receiver and subsequently uploaded to a remote server via a phone application for analysis and review.

Two investigators (K.J.B., J.J.) blinded to the results of the WMC studies independently reported the gas-sensing capsule transit studies. A third assessor (A.F.C.) adjudicated disparate results. Ingestion and excretion were defined the same as for the WMC. As shown in Table 1, three parameters were used to detect the GDJ and two for the ICJ. GET, SBTT and CTT were thereafter calculated as described earlier.

2.5 | Endpoints

The endpoints measured included times from ingestion to when the landmarks (GDJ, ICJ and excretion) were identified by signals from each capsule and the differences between the two capsules; and regional and WGTTs for each capsule and the differences between the two capsules; interobserver agreements of landmarks for both capsules; and safety and tolerability.

2.6 | Statistical analysis

As this was a pilot study, formal power calculations were not possible. A sample size of approximately 20 studies with complete data for both the primary and validation cohorts and 20 for the tandem gas-sensing capsule study were planned. The distributions of continuous data were assessed using the Shapiro–Wilk test with 95% confidence interval. Descriptive statistics of regional transit times were reported as median and interquartile range (IQR) unless otherwise stated. Regional

TABLE 1 Comparison of the methods of landmark assessment between gas-sensing capsule and wireless motility capsule

'Landmark'	Gas-sensing capsule	Wireless motility capsule
Entry to the stomach	• Increase in recorded temperature from ambient to body temperature	
Passage from stomach to duodenum (gastroduodenal junction)	• Increase in carbon dioxide concentration • Change in capsule orientation • Detection of a change in electromagnetic properties of the environment adjacent to the capsule	• Sharp rise in pH (>3 units) from gastric baseline or to a pH of greater than 4 pH units
Passage from ileum to caecum (ileocaecal junction)	• Change in volatile organic compound sensor conductance (specifically related to reduced oxygen and increased volatile organic compound production) • Step change in the electromagnetic properties of the capsule environment corresponding to the ileum and the caecum	• Fall of ≥1 pH unit distal to gastric emptying (by at least 30 min) and lasting for at least 10 min
Excretion	• Loss of signal or drop in temperature corresponding to a bowel motion	

transit times were assessed using Wilcoxon matched-pairs signed rank test, stratified by capsule type in the primary and validation cohorts to assess the effect of order of ingestion on transit. The relationship between paired values was examined by creating regression scatterplots enabling both calculation of the Spearman correlation coefficient and evaluation of heteroscedasticity.[24] Agreement between the two devices was explored using Bland–Altman plots with 95% limits of agreement. Bootstrapping was performed to confirm confidence intervals. Interobserver agreement was assessed using intraclass correlation coefficient (ICC). Intrasubject variation was evaluated using the coefficient of variation (root mean square method). Exact McNemar's test for paired proportions was used to compare the proportion of landmarks detected by each device. A $p \leq 0.05$ was considered statistically significant. Univariate and multivariate analyses of times were performed using Cox regression. All statistical analysis was performed using Stata/SE version 16.1 (StataCorp LP) and GraphPad Prism 9.3.0. All authors had access to the study data and reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Subjects

The demographics for the three cohorts studied are shown in Table 2. While there were no statistically significant differences between the primary cohort (tandemly ingested gas-sensing capsule and WMC) and the tandem gas-sensing capsule cohort, the validation (tandemly ingested gas-sensing capsule and WMC) cohort differed in terms of country of origin, gender, age and BMI.

3.2 | Signal generation

Overlays of typical graphs generated from both capsules are shown in Figure 1. While there was no clinically significant interference overall noted between the signal captured for the two capsules, there were occasional missed packets of data transmission in the gas-sensing capsule and WMC.

Successful identification of the GDJ and ICJ in the 50 studies in which the gas-sensing capsule and WMC were tandemly ingested is shown in Table 3 according to the cohort. The GDJ was identifiable in 92% of the gas-sensing capsule studies versus 82% of the WMC studies ($p = 0.27$) and the ICJ in 96% versus 84%, respectively ($p = 0.11$). Thus, for the WMC, the GDJ was not able to be identified in 18% and the ICJ in 16%. Most were due to prolonged signal loss, one was excluded due to protocol deviation due to early food ingestion and one was excluded due to non-physiological GET. For the gas-sensing capsule, the GDJ was not identifiable in 8% related to signal loss ($n = 2$), exclusion due to protocol deviation due to early food ingestion ($n = 1$) and exclusion due to non-physiological GET ($n = 1$). The ICJ was not identifiable in 4% related to cloud outage (entirety of one study and for part of another). Five participants required an x-ray to confirm capsule excretion, although one participant declined ($n = 2$ WMC, $n = 2$ gas-sensing capsule, $n = 1$ both capsules). In the tandem gas-sensing capsule study, two gas-sensing capsules (in different participants) prematurely lost signal due to battery failure during colonic transit and underwent abdominal x-ray.

3.3 | Interobserver agreement in defining landmarks

The agreement of individual raters in defining the landmarks is shown in Table 4. Agreement was excellent for the WMC.[22,25] The ICC was also excellent for the evaluation of the GDJ (ICC: 0.99 [0.98–0.99]) and ICJ (0.97 [0.95–0.99]) by the two independent reporters for the gas-sensing capsule.

3.4 | Comparison of transit times of the gas-sensing and WMCs

The transit times calculated by tandemly ingested WMC and gas-sensing capsules were similar (Table 5). The scatter of differences

TABLE 2 Demographics of the primary and validation cohorts and the tandem gas-sensing capsule cohort

	Tandem gas-sensing and wireless motility capsule cohorts		
	Primary cohort	Validation cohort	Tandem gas-sensing capsule cohort
n	26	24	20
Male gender	16 (62%)[a]	6 (25%)[a]	14 (70%)
Age (y)	35 (31-39)[b]	25 (23-30)[b]	35 (29–39)
BMI (kg/m^2)	25 (22-28)[c]	22 (20-23)[c]	24 (22–26)
Non-smoker, *n*	26 (100%)	24 (100%)	20 (100%)
Country of residence	Australia	New Zealand	Australia ($n = 16$) and New Zealand ($n = 4$)

[a]$p = 0.01$; [b]$p < 0.0003$; [c]$p = 0.0014$.

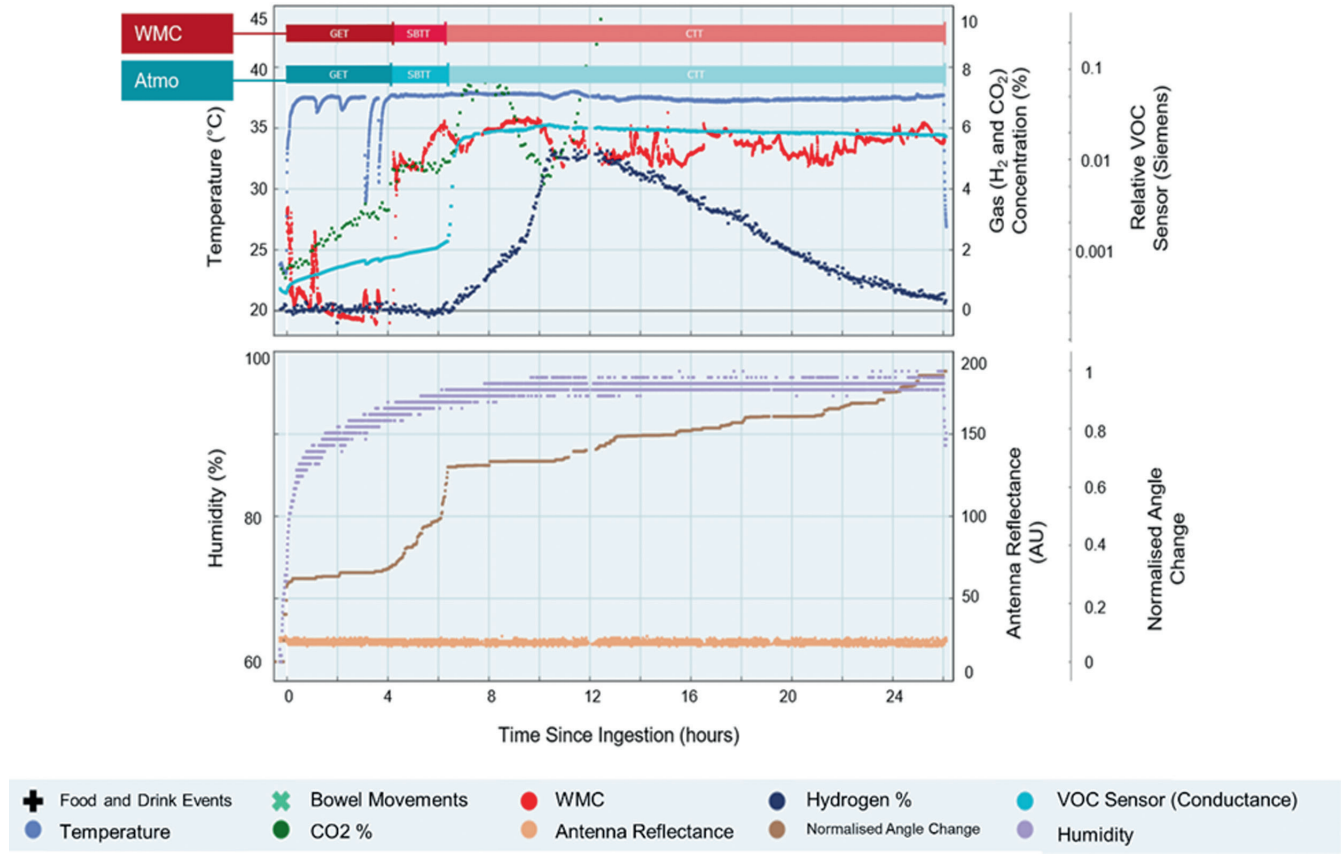

FIGURE 1 Gas-sensing capsule and wireless motility capsule data overlay. Comparative transit times recorded are illustrated in the trace in red and aqua at the top of the figure.

TABLE 3 Landmark identification according to capsules for which signals were successfully transmitted and captured in the primary and validation cohorts

	Wireless motility capsule		Gas-sensing capsule		Paired identification[a]
Landmark	Number	Measurable	Number	Measurable	Number
Primary cohort					
Gastroduodenal junction	26	21[b]	26	25[b]	21
Ileocaecal junction	26	24	26	26	24
Capsule exit	26	26	26	25	25
Validation cohort					
Gastroduodenal junction	24	20[b]	24	21[c,d]	19
Ileocaecal junction	24	18	24	22[d]	17
Capsule exit	24	21	24	22[e]	20

[a]Both capsules able to identify landmark.
[b]Gastroduodenal junction excluded due to non-physiological gastric emptying time.
[c]Gastroduodenal junction assessment was excluded due to apparent food intake during the 6 h fast. Others missing due to data loss.
[d]Two gas-sensing capsule data not collected due to cloud system outage.
[e]Cloud outage restored in time to confirm one capsule exit.

for individual subjects is shown in Figure 2. Transit time was not affected by order of ingestion (data not shown). Both capsules were passed in the same bowel motion in 17 out of 26 eligible studies (65%). Of the remaining nine studies, the WMC passed first in four participants, the gas-sensing capsule passed first in four participants and in one study the order of excretion could not

TABLE 4 Intraclass correlation coefficients and transit time values for each region of interest as calculated blindly by the investigators for the wireless motility capsule and the gas-sensing capsule

Regional transit time	Wireless motility capsule ($n = 26$)			Gas-sensing capsule ($n = 26$)		
		Mean transit time, h (95% CI)	Intraclass correlation coefficient (95% CI)		Mean transit time, h (95% CI)	Intraclass correlation coefficient (95% CI)
Gastric emptying time	Rater 1	3.3 (1.9–4.6)	0.999 (0.998–1.00)	Rater 3	2.55 (2.16–2.95)	0.99 (0.98–0.99)
	Rater 2	3.6 (1.9–4.5)		Rater 4	2.5 (2.13–2.91)	
Orocaecal transit time	Rater 1	7.5 (5.9–9.2)	0.989 (0.974–0.995)	Rater 3	6.8 (6.2–7.4)	0.97 (0.95–0.99)
	Rater 2	7.6 (6.0–9.3)		Rater 4	6.7 (6.2–7.3)	
Colonic transit time	Rater 1	20.7 (13.8–27.5)	0.990 (0.990–1.000)	Rater 3	25.0 (15.7–34.3)	1.00
	Rater 2	20.5 (13.7–27.4)		Rater 4	25.0 (15.7–34.3)	
Whole gut transit time	Rater 1	30.3 (23.4–37.2)	0.997 (0.993–0.998)	Rater 3	31.7 (22.2–41.3)	1.00
	Rater 2	30.6 (23.7–37.5)		Rater 4	31.7 (22.2–41.2)	

Note: The rater number denotes an individual rater. Intraclass correlation coefficient values approaching 1.0 demonstrate greater reliability (poor: <0.40; fair: 0.40–0.59; good: 0.60–0.74; excellent: 0.75–1.00).[22]

TABLE 5 Comparison of transit times, shown as median (IQR) in hours, for the gas-sensing capsules and the tandemly ingested wireless motility capsule in the primary and validation cohorts, and for tandemly ingested gas-sensing capsules. The coefficient of variation (CV) is also shown. Paired data were evaluated with a Wilcoxon matched-pairs signed rank test

Region	n	Transit times (h)		p-value	Differences in transit times (h)	CV (%)
		Wireless motility capsule	Gas-sensing capsule			
Primary cohort						
Gastric emptying	21	2.5 (2.1–3.5)	2.4 (2.0–3.5)	0.24	−0.003 (−0.32 to −0.04)[a]	15
Small bowel	21	4.7 (3.8–5.2)	4.5 (3.9–4.9)	0.48	−0.02 (−0.35 to 0.19)	17
Orocaecal	24	7.3 (6.5–8.3)	6.7 (6.2–7.8)	0.17	−0.02 (−0.78 to −0.09)	13
Colon	23	19.7 (15.7–25.0)	20.0 (9.2–29.2)	0.15	0.09 (−0.05 to 2.10)	28
Whole	25	26.1 (24.0–36.5)	26.9 (17.6–42.5)	0.21	0.02 (−0.05 to 0.25)	24
Validation cohort						
Gastric emptying	19	2.5 (2.0–2.85)	2.5 (2.0–2.9)	>0.99	0.070 (−0.32 to 0.17)	14
Small bowel	15	4.6 (3.8–5.6)	4.8 (3.7–6.8)	0.30	0.32 (−0.2 to 0.87)	13
Orocaecal	17	7.7 (6.0–9.6)	7.8 (6.0–9.9)	0.46	0.1 (−0.26 to 0.25)	7
Colon	14	19.0 (16.6–28.2)	20.0 (14.8–38.8)	0.49	−0.07 (−1.93 to 0.46)	27
Whole gut	20	26.9 (23.9–44.1)	25.8 (23.5–44.1)	0.62	0.005 (−0.88 to 0.024)	19
	n	Capsule 1	Capsule 2	p-value	Differences in transit times (h)	CV (%)
Tandem gas-sensing capsule cohort						
Gastric emptying	18	2.4 (2.2–4.0)	2.5 (2.0–3.5)	0.19	−0.08 (−0.74–0.18)[b]	34
Small bowel	17	4.4 (3.4–5.0)	4.2 (3.3–5.3)	0.53	−0.03 (−0.52–0.19)	11
Orocaecal	19	6.9 (6.3–8.8)	6.7 (6.0–8.8)	0.68	0.17 (−0.14–0.31)	21
Colon	17	20.2 (16.4–38.7)	19.2 (16.1–31.2)	0.89	0.18 (−1.25–1.37)	35
Whole gut	18	26.5 (23.6–47.5)	26.2 (23.6–47.7)	0.71	−0.005 (−0.04–0.05)	29

[a]Transit time for the gas-sensing minus wireless motility capsules.

[b]Transit time for the first ingested minus the second ingested gas-sensing capsules.

be determined. Regression analysis showed the paired data were linearly related, that the Spearman correlation coefficient was statistically significant for all indices and that heteroscedasticity was not evident (Figure 3).[26] Bland–Altman plots showed agreement between the two devices for the assessment of the calculated transit times (Figure 4 and Table 6).

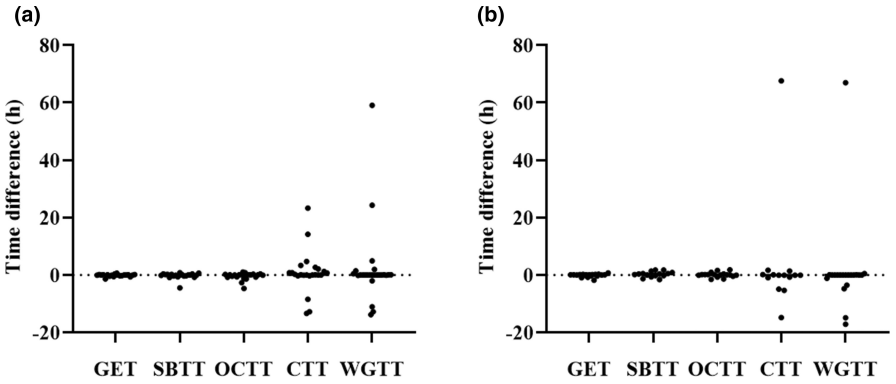

FIGURE 2 Differences (gas-sensing capsule minus wireless motility capsule) in gastric emptying time (GET), small bowel transit time (SBTT), orocaecal transit time (OCTT), colonic transit time (CTT) and whole gut transit time (WGTT) in individual patients for a. the primary cohort; and B. the validation cohort.

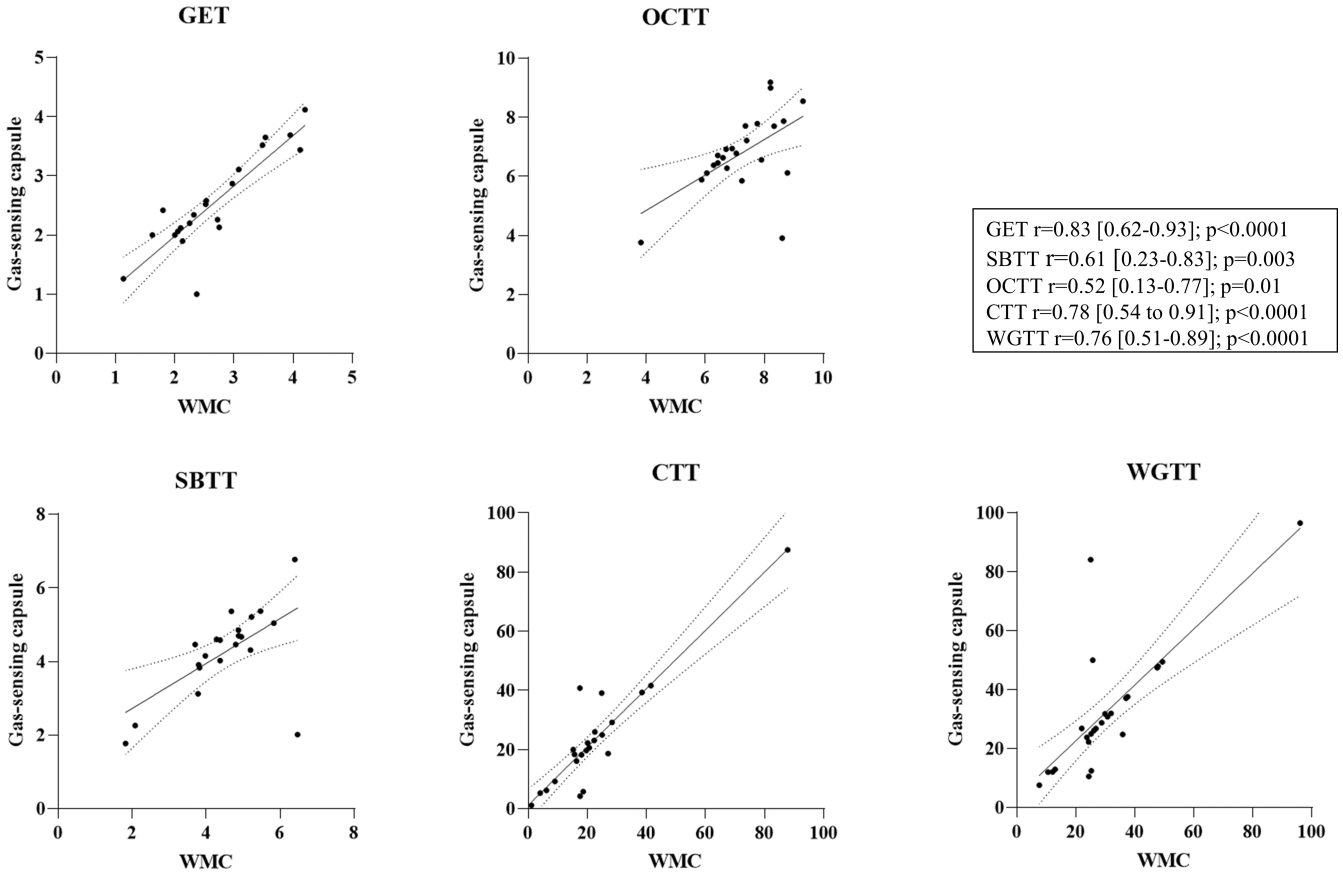

FIGURE 3 Correlation (with 95% confidence interval and line of fit) between gastric emptying time (GET), small bowel transit time (SBTT), orocaecal transit time (OCTT), colonic transit time (CTT) and whole gut transit time (WGTT) for paired gas-sensing capsule and wireless motility capsule (WMC) in the primary cohort. Spearman correlation coefficients (95% CI) are shown in the box.

In the validation cohort, in which 15 of the 24 participants (63%) ingested the gas-sensing capsule first and 14 (out of 20 assessable capsules, 70%) were passed simultaneously, there were no statistically significant differences in transit times obtained by each capsule (Table 5). The differences in transit times between the two capsules for individual subjects was minimal (Table 5 and Figure 2). Transit time was not affected by ingestion order. Bland–Altman plots illustrated an agreement between the two devices that was similar to that in the primary cohort (Figure 4, Table 6).

3.5 | Variation in transit with gas-sensing capsule tandem ingestion

To determine the intrasubject variability in capsule transit, tandem ingestion of two gas-sensing capsules was assessed in 20 subjects. Excretion in the same bowel motion occurred in 12 out of 18 assessable studies (67%) (two unknown due to battery failure). Paired data that were evaluable for GET and orocaecal transit time (OCTT) occurred in 18 and 19 participants, respectively. The time to reach the key landmarks varied between the tandemly

ingested gas-sensing capsules as shown in Table 5. There were no significant differences between the transit times and minimal median time differences between the transit times overall (18 s for WGTT). The coefficient of variation for individual measurements is outlined in Table 5.

3.6 | Safety and tolerability

All participants were able to swallow both capsules. In the first study, symptoms were documented in six participants and described as mild. They comprised abdominal pain ($n = 2$), headache ($n = 3$), and throat discomfort related to WMC ingestion ($n = 1$). All symptoms, except the headache, were assessed as possible or likely to have been related to the capsules. In the validation cohort, no adverse symptoms were reported. Symptom data was provided by 17 participants (85%) in the tandem gas-sensing capsule study and comprised abdominal pain ($n = 1$), bloating ($n = 1$) and throat discomfort ($n = 1$). All were mild. There were no episodes of capsule retention and the capsules passed spontaneously without the need for intervention in all participants.

4 | DISCUSSION

Assessment of gastrointestinal transit in routine clinical practice has been limited to date due to several issues that include cumbersome imaging with radiation exposure, heterogeneous protocols and high cost. The introduction of the WMC has shown that patient-friendly and safe telemetric techniques can provide an alternative method of regional and whole gut transit assessment. With validation against currently accepted methodologies that include scintigraphy and radio-opaque markers, the WMC was approved by the Food and Drug Administration for assessment of patients with chronic constipation and gastroparesis.[6,7,27] In the present study, the performance of the novel gas-sensing capsule was compared with the WMC in healthy adult subjects. Unlike the WMC, which uses changes in pH to identify critical landmarks to enable regional transit calculations, the gas-sensing capsule uses alternative characteristics that are based on physical properties and chemical analysis by the capsule. The key findings were that the whole gut transit of the gas-sensing capsule was similar to that of the WMC and that the definitions for the gas-sensing capsule-derived landmarks are highly reproducible. Additionally, regional transit times correlated very well with those previously defined by the WMC in prospective studies and were within the biological variance of the passage of capsules through the gastrointestinal tract, as highlighted in the tandem gas-sensing capsule study. Furthermore, the gas-sensing capsule was readily ingested, well-tolerated and technically reliable.

Critical to the validity of the gas-sensing capsule in measuring regional transit times is the accuracy of defining key landmarks of the GDJ, ICJ and excretion. The same methods were used by both capsules to determine the capsule's time of entry and exit from the gastrointestinal tract. However, capsule exit could not always be confirmed and did necessitate plain abdominal X-ray in a few participants to document excretion. Key to validating the gas-sensing capsule was how it performed when defining the GDJ and ICJ. The WMC uses intraluminal pH variations along the gastrointestinal tract, where an abrupt rise in pH from the acidic gastric environment to the basic proximal small bowel environment signals gastric emptying, after which a gradual increase in pH along the small bowel is seen, followed by an abrupt drop in pH corresponding to fermentative generation of weak organic acids, especially short-chain fatty acids, representing entry into the proximal colon.[13,21] By contrast, the gas-sensing capsule uses multiple measures. That is, the GDJ is identified by abrupt changes in carbon dioxide (produced as a by-product of acid–base reactions in the duodenum) in conjunction with changes in temperature, capsule orientation and physical electromagnetic properties of the environment surrounding the capsule. The ICJ is identified by changes in volatile organic compound sensor conductance (specifically related to reduced oxygen and increased volatile organic compound production) and step-change in the electromagnetic properties of the capsule environment. Despite the different methods of landmark identification, there was minimal interobserver variance observed, and the median times for the GDJ and ICJ differed by less than 2 min in the primary cohort and less than 6 min in the validation cohort. The agreement between paired calculations for each device was evaluated by Bland–Altman analyses, which show graphically the agreement between two devices, and is statistically expressed as the bias, which approaches zero in devices with perfect agreement, in addition to 95% limits of agreement.[28] In the current study, the bias between the WMC and gas-sensing capsules was measured in minutes, which is clinically acceptable. However, the interpretation of the limits of agreement would be facilitated by a better understanding of physiological variation of capsule transit through the gastrointestinal tract.

Hence, two gas-sensing capsules were ingested in tandem to evaluate the variation in time a capsule might spend within the various regions of the gastrointestinal tract, independently of external variables such as dietary intake, stress or related to inherent differences in the capsule's physical characteristics. The median times to reach the landmarks and hence the calculated regional transit times were very closely aligned (Table 5). The CV of the two gas-sensing capsule measurements ranged from 11% to 35% and was similar to those calculated for the primary and validation cohorts. Furthermore, the bias and limits of agreement from the Bland–Altman analyses

FIGURE 4 Bland–Altman plots. Transit difference for gastric emptying time (GET), small bowel transit time (SBTT), orocaecal transit time (OCTT), colonic transit time (CTT) and whole gut transit time (WGTT) between paired devices (gas-sensing capsule minus wireless motility capsule) over the average of transit time with 95% level of agreement shown in the red dotted line and mean difference at the black dotted line. Single extreme outlier excluded from gastric emptying time and orocaecal transit time related to a GET of 17 h.

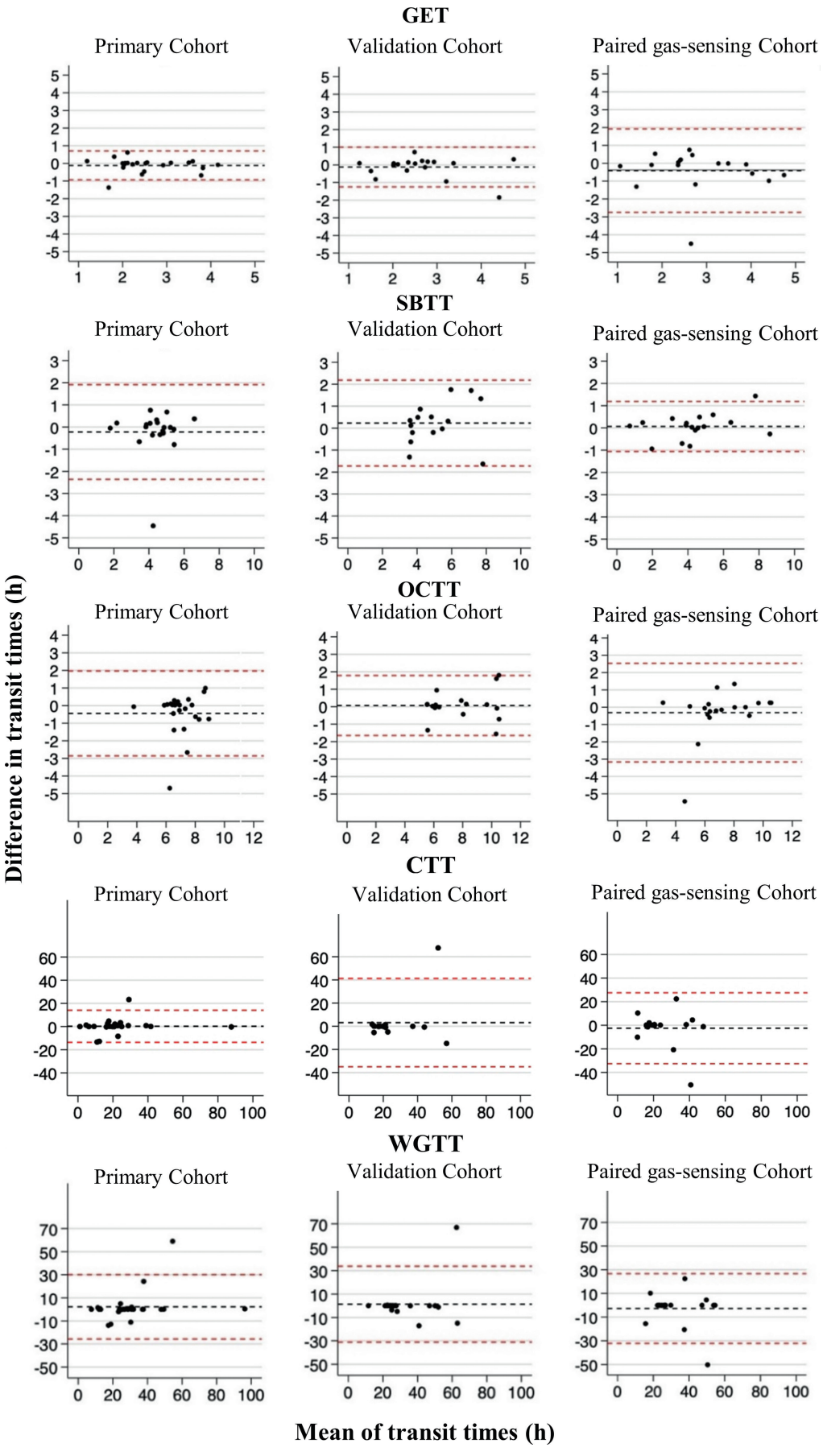
GET
Primary Cohort
Validation Cohort
Paired gas-sensing Cohort
SBTT
Primary Cohort
Validation Cohort
Paired gas-sensing Cohort
OCTT
Primary Cohort
Validation Cohort
Paired gas-sensing Cohort
CTT
Primary Cohort
Validation Cohort
Paired gas-sensing Cohort
WGTT
Primary Cohort
Validation Cohort
Paired gas-sensing Cohort
Difference in transit times (h)
Mean of transit times (h)

TABLE 6 Bias (95% limits of agreement) in hours on Bland–Altman analysis for regional transit times for the studied cohorts

	Wireless motility vs gas-sensing capsules		
Regional transit time	**Primary cohort**	**Validation cohort**	**Paired gas-sensing cohort**
Gastric emptying time	−0.12 (−0.94 to 0.70)	−0.12 (−1.25 to 1.00)	−0.415 (−2.749 to 1.920)
Small bowel transit time	−0.22 (−2.36 to 1.92)	0.23 (−1.72 to 2.19)	0.07 (−1.06 to 1.19)
Orocaecal transit time	−0.45 (−2.86 to 1.97)	0.07 (−1.65 to 1.79)	−0.32 (−3.17 to 2.53)
Colonic transit time	0.21 (−13.61 to 14.04)	3.13 (−34.97 to 41.22)	−2.53 (−32.59 to 27.52)
Whole gut transit time	2.19 (−25.70 to 30.08)	1.30 (−31.13 to 33.73)	−2.74 (−32.19 to 26.71)

were similar to those between the WMC and gas-sensing capsule. Our interpretation, therefore, is that the limits of agreement between the two devices in identifying the GDJ and ICJ were clinically satisfactory and accounted for by physiological factors rather than differences in accuracy in detecting the landmarks.

Such physiological variance around regional transit times for a swallowed capsule has been indirectly addressed for the WMC previously by repeated ingestions over time as well as in other studies, which suggest that variation is not insignificant and that its magnitude varies by region in the gastrointestinal tract.[21,29] In a WMC validation study, coefficients of variation (CV) between 20% and 42% for all transit regions were observed when WMC ingestions were repeated at 2- or 4-week intervals in the same individual.[29] Intrasubject variability was particularly notable for GET, where the CV was greatest between the WMCs ingested 2 weeks apart (40%) and for CTT in which the CV was greatest for the 4-week ingestion (42%).[29] In studies performed 24 h apart, intrasubject CV for CTT was greater than for the SBTT (26% vs 12%, respectively).[21] This regional variability has also been observed with conventional scintigraphic techniques and other ingestible capsules measuring gastrointestinal transit.[30,31] The study by Haase et al. reported a CV of 20% for GET and SBTT, 45% for CTT and 35% for WGTT when two magnetic tracking capsules were ingested over two consecutive days.[20] Similarly, for scintigraphy, CVs of 19% and 28% were reported for SBTT and CTT and for lactulose-hydrogen breath testing, a CV up to 28% for OCTT was reported.[30,31] In keeping with these studies, the current study revealed a CV range of 13%–28% in the primary cohort and 7%–27% in the validation cohort. Smaller variation in SBTT has been previously observed and postulated to be related to tighter physiological regulation of small bowel function and/or reduced sensitivity of fibre compared with the colon.[21] The greater variation in CTT within subjects potentially relates to differences in capsule excretion time, which is readily understandable since bowel actions were usually separated by several hours and the two capsules were passed in different bowel actions in almost a quarter of subjects. CTT may be affected by bowel frequency and completeness of bowel emptying and potentially influenced by colonic regional motility variability (affected by dietary factors such as fibre content) and diurnal variability, with slower colonic transit observed overnight.[32,33]

The study did not uncover any safety concerns, as would be expected in a cohort of medically screened, healthy volunteers. There was no retention of either capsule, although some participants required X-ray to confirm excretion. Mild symptoms were reported at low rates. Whether these were related to the ingestion of two capsules in tandem, related to a single capsule itself or completely unrelated to the capsules cannot be determined. The only unequivocal capsule-specific adverse effect was mild throat discomfort in two subjects.

Signal interference between the two ingested capsules leading to data loss did not appear to occur despite both capsules transmitting data at a similar frequency. The intervals between transmission of data are different between the two devices and so there was low probability of the transmissions coinciding and leading to data loss. However, signal issues were experienced intermittently with the WMC, particularly in the validation cohort, although the reasons for this remain unclear. Thus, identification of the ICJ was not possible in a quarter of subjects and gastroduodenal transit could not be identified in 18% of subjects. Such difficulties have been experienced by other investigators. Data loss and/or non-informative pH changes preventing recognition of the GDJ and/or ICJ have been reported in between 2% and 15% in various studies.[67101112] Full data loss rates have also varied between 3% and 7%.[10,11] Such difficulties may, at least in part, be related to the nature of the pH sensor and its sensitivity to environmental electromagnetic radiation.[8] Such issues were not experienced with the gas-sensing capsule by virtue of its chemosensor with high signal-to-noise ratio and the fact that the additional physical properties also supported recognition of movement from stomach to duodenum and ileum to caecum. The few failures of the gas-sensing capsule were related to technical failures associated with battery failure and outage of the cloud, for which mitigation procedures were introduced into the manufacturing process to avoid similar issues in future gas-sensing capsule studies.

Advantages of the gas-sensing capsule over the WMC, beyond the tendency to be more reliable in identifying landmarks, include the potential to provide additional information related to its ability to measure concentrations of specific gases and volatile organic compounds. Such potential to define, for example, local microbial fermentative activity by virtue of hydrogen concentrations is currently being explored with preliminary observations in an intervention study of patients with irritable bowel syndrome that the regional distribution of colonic fermentation and its manipulation by changes in types of fibre ingested can be defined using the gas-sensing capsule.[34] By contrast, colonic luminal pH profiles with the WMC did not identify such changes to fermentation patterns. The ability to document microbial activity offers an opportunity to define abnormal fermentation in the small bowel and, therefore, to document small intestinal bacterial overgrowth. In other words, the gas-sensing capsule has the potential to offer unique diagnostic and monitoring information to regional gastrointestinal transit times.

The strengths of the study included the use of a reference standard (WMC) that has been previously compared to conventional techniques for assessing transit; the blinding of the assessment and reporting of regional and whole gut transit of WMC and gas-sensing capsule; implementation of a standardised protocol, including morning capsule ingestion to account for diurnal variation in colonic transit; and the inclusion of a validation cohort. Additionally, the assessment of variation independently of external influencing factors through tandem gas-sensing capsule ingestion, which has not been reported with the WMC, provided novel and important information about the biological variation in gastrointestinal tract transit of a capsule within an individual. The limitations of the current study include the relatively small size of the cohort, which will limit its generalisability. However, it is reassuring that the two healthy cohorts, which were demographically different according to gender, age, BMI and country of residence, showed similar findings.

In conclusion, the gas-sensing capsule is a safe and well-tolerated ambulatory test to assess regional and whole gut transit in healthy subjects. Agreement of transit times between the gas-sensing capsule and the WMC devices was judged to be very good in both the primary and validation cohorts. Differences in transit times in individuals are likely to represent biological variation rather than differences in measured landmarks since similar variation was observed when two gas-sensing capsules were ingested in tandem. Future studies are needed to assess the performance of the gas-sensing capsule in subjects with altered gut physiology and/or dysmotility.

AUTHOR CONTRIBUTIONS

Phoebe A Thwaites: Data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); project administration (lead); writing – original draft (lead); writing – review and editing (lead). **Chu K Yao:** Data curation (equal); formal analysis (equal); project administration (supporting); writing – review and editing (supporting). **Jasjot Maggo:** Data curation (supporting); project administration (supporting); writing – review and editing (supporting). **James John:** Formal analysis (supporting); software (supporting); writing – review and editing (supporting). **Adam F Chrimes:** Formal analysis (equal); software (equal); writing – review and editing (supporting). **Kourosh Kalantar-zadeh:** Conceptualization (equal); formal analysis (supporting); writing – review and editing (supporting). **Francis C Parker:** Formal analysis (lead); software (lead); writing – original draft (supporting). **Rebecca Burgell:** Formal analysis (supporting); supervision (supporting); writing – review and editing (supporting). **Jane G Muir:** Writing – review and editing (supporting). **Daniel So:** Project administration (supporting); writing – review and editing (supporting). **Richard B Gearry:** Supervision (supporting); writing – review and editing (supporting). **Kyle J Berean:** Formal analysis (equal); methodology (equal); software (equal); writing – review and editing (supporting). **Peter Gibson:** Conceptualization (lead); formal analysis (equal); funding acquisition (lead); methodology (equal); supervision (equal); writing – original draft (supporting); writing – review and editing (lead).

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REFERENCES

1. Saad RJ, Hasler WL. A technical review and clinical assessment of the wireless motility capsule. Gastroenterol Hepatol (N Y). 2011;7(12):795–804.
2. Arora Z, Parungao JM, Lopez R, Heinlein C, Santisi J, Birgisson S. Clinical utility of wireless motility capsule in patients with suspected multiregional gastrointestinal dysmotility. Dig Dis Sci. 2015;60(5):1350–7.

3. Maurer AH. Enhancing scintigraphy for evaluation of gastric, small bowel, and colonic motility. Gastroenterol Clin North Am. 2020;49(3):499–517.
4. Abrahamsson H, Antov S. Accuracy in assessment of colonic transit time with particles: how many markers should be used? Neurogastroenterol Motil. 2010;22(11):1164–9.
5. Bharucha AE, Anderson B, Bouchoucha M. More movement with evaluating colonic transit in humans. Neurogastroenterol Motil. 2019;31(2):e13541.
6. Kuo B, McCallum RW, Koch KL, Sitrin MD, Wo JM, Chey WD, et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. Aliment Pharmacol Ther. 2008;27(2):186–96.
7. Rao SS, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol. 2009;7(5):537–44.
8. Kalantar-zadeh K, Fry B. Nanotechnology-enabled sensors. New York: Springer; 2008.
9. Yang Y, Gao W. Wearable pH sensing beyond the Nernst limit. Nature Electronics. 2018;1(11):580–1.
10. Wang YT, Mohammed SD, Farmer AD, Wang D, Zarate N, Hobson AR, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. Aliment Pharmacol Ther. 2015;42(6):761–72.
11. Hasler WL, May KP, Wilson LA, van Natta M, Parkman HP, Pasricha PJ, et al. Relating gastric scintigraphy and symptoms to motility capsule transit and pressure findings in suspected gastroparesis. Neurogastroenterol Motil. 2018;30(2):e13196.
12. Lee AA, Rao S, Nguyen LA, Moshiree B, Sarosiek I, Schulman MI, et al. Validation of diagnostic and performance characteristics of the wireless motility capsule in patients with suspected gastroparesis. Clin Gastroenterol Hepatol. 2019;17(9):1770–1779 e1772.
13. Zarate N, Mohammed SD, O'Shaughnessy E, Newell M, Yazaki E, Williams NS, et al. Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique. Am J Physiol Gastrointest Liver Physiol. 2010;299(6):G1276–86.
14. So D, Yao CK, Ardalan ZS, Thwaites PA, Kalantar-Zadeh K, Gibson PR, et al. Supplementing dietary fibers with a low FODMAP diet in irritable bowel syndrome: a randomized controlled crossover trial. Clin Gastroenterol Hepatol. 2022;20:2112–21.
15. Berean KJ, Ha N, Ou JZ, Chrimes AF, Grando D, Yao CK, et al. The safety and sensitivity of a telemetric capsule to monitor gastrointestinal hydrogen production in vivo in healthy subjects: a pilot trial comparison to concurrent breath analysis. Aliment Pharmacol Ther. 2018;48(6):646–54.
16. Kalantar-Zadeh K, Yao CK, Berean KJ, Ha N, Ou JZ, Ward SA, et al. Intestinal gas capsules: a proof-of-concept demonstration. Gastroenterology. 2016;150(1):37–9.
17. Kalantar-zadeh K, Ha N, Ou JZ, Berean KJ. Ingestible Sensors. ACS Sensors. 2017;2(4):468–83.
18. Ou JZ, Cottrell JJ, Ha N, Pillai N, Yao CK, Berean KJ, et al. Potential of in vivo real-time gastric gas profiling: a pilot evaluation of heat-stress and modulating dietary cinnamon effect in an animal model. Sci Rep. 2016;6:33387.
19. Kalantar-Zadeh K, Berean, K.J., Ha, N., Chrimes, A.F., Xu, K., Grando, D., et al. A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut Nature Electronics 2018;1(Issue 1):79–87.
20. Haase AM, Gregersen T, Schlageter V, Scott MS, Demierre M, Kucera P, et al. Pilot study trialling a new ambulatory method for the clinical assessment of regional gastrointestinal transit using multiple electromagnetic capsules. Neurogastroenterol Motil. 2014;26(12):1783–91.
21. Mikolajczyk AE, Watson S, Surma BL, Rubin DT. Assessment of tandem measurements of pH and total gut transit time in healthy volunteers. Clin Transl Gastroenterol. 2015;6:e100.
22. Farmer AD, Wegeberg AL, Brock B, Hobson AR, Mohammed SD, Scott SM, et al. Regional gastrointestinal contractility parameters using the wireless motility capsule: inter-observer reproducibility and influence of age, gender and study country. Aliment Pharmacol Ther. 2018;47(3):391–400.
23. Sarosiek I, Selover KH, Katz LA, Semler JR, Wilding GE, Lackner JM, et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Aliment Pharmacol Ther. 2010;31(2):313–22.
24. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg. 2018;126(5):1763–8.
25. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016;15(2):155–63.
26. Dancey C, Reidy J. Statistics without Maths for psychology: using SPSS for windows. London: Prentice Hall; 2004.
27. Camilleri M, Thorne NK, Ringel Y, Hasler WL, Kuo B, Esfandyari T, Gupta A, Scott SM, Mccallum RW, Parkman HP, Soffer E, Wilding GE, Semler JR, Rao SS Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation. Neurogastroenterol Motil 2010;22(8):874–882, e233.
28. Giavarina D. Understanding Bland Altman analysis. Biochem Med (Zagreb). 2015;25(2):141–51.
29. Diaz Tartera HO, Webb DL, Al-Saffar AK, Halim MA, Lindberg G, Sangfelt P, et al. Validation of SmartPill([R]) wireless motility capsule for gastrointestinal transit time: intra-subject variability, software accuracy and comparison with video capsule endoscopy. Neurogastroenterol Motil. 2017;29(10):1–9.
30. Cremonini F, Mullan BP, Camilleri M, Burton DD, Rank MR. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. Aliment Pharmacol Ther. 2002;16(10):1781–90.
31. La Brooy SJ, Male PJ, Beavis AK, Misiewicz JJ. Assessment of the reproducibility of the lactulose H2 breath test as a measure of mouth to caecum transit time. Gut. 1983;24(10):893–6.
32. Wyman JB, Heaton KW, Manning AP, Wicks AC. Variability of colonic function in healthy subjects. Gut. 1978;19(2):146–50.
33. Notghi A, Hutchinson R, Kumar D, Tulley N, Harding LK. Use of geometric center and parametric images in scintigraphic colonic transit studies. Gastroenterology. 1994;107(5):1270–7.
34. So D, Yao C, Gibson P, Muir J. Combination of two fibers with different fermentabilities in patients with irritable bowel syndrome initiated on a low-FODMAP diet is well tolerated and promotes distal colonic fermentation, as shown telemetrically by colonic hydrogen concentrations but not pH. J Gastroenterol Hepatol. 2021;36(Suppl 3):160–1.

SUPPORTING INFORMATION

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

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