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Review

Bioelectrical Signals for the Diagnosis and Therapy of Functional Gastrointestinal Disorders

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Abstract: Coordinated contractions and motility patterns unique to each gastrointestinal organ facilitate the digestive process. These motor activities are coordinated by bioelectrical events, sensory and motor nerves, and hormones. The motility problems in the gastrointestinal tract known as functional gastrointestinal disorders (FGIDs) are generally caused by impaired neuromuscular activity and are highly prevalent. Their diagnosis is challenging as symptoms are often vague and difficult to localize. Therefore, the underlying pathophysiological factors remain unknown. However, there is an increasing level of research and clinical evidence suggesting a link between FGIDs and altered bioelectrical activity. In addition, electroceuticals (bioelectrical therapies to treat diseases) have recently gained significant interest. This paper gives an overview of bioelectrical signatures of gastrointestinal organs with normal and/or impaired motility patterns and bioelectrical therapies that have been developed for treating FGIDs. The existing research evidence suggests that bioelectrical activities could potentially help to identify the diverse etiologies of FGIDs and overcome the drawbacks of the current clinically adapted methods. Moreover, electroceuticals could potentially be effective in the treatment of FGIDs and replace the limited existing conventional therapies which often attempt to treat the symptoms rather than the underlying condition.

Keywords: functional gastrointestinal disorders; bioelectrical signals; slow waves; bioelectrical therapies; electroceuticals

1. Introduction

The gastrointestinal (GI) tract is responsible for the digestion and nutrient absorption of food we ingest. The GI tract is composed of multiple organs, including the oropharynx, esophagus, stomach, and small and large intestine, each with its own specialized anatomy, properties and function, as illustrated in Figure 1. The process of digestion starts in the mouth, where food particles are propelled through the pharynx into the stomach via the esophagus. The stomach mechanically and chemically breaks and mixes the food with the help of contractions, gastric acids, and enzymes. The small intestine breaks the food into even smaller components, absorbs the nutrients, and transfers the remaining contents to the large intestine. In the large intestine, water is absorbed, and the contents are prepared for expulsion through the rectum [1].

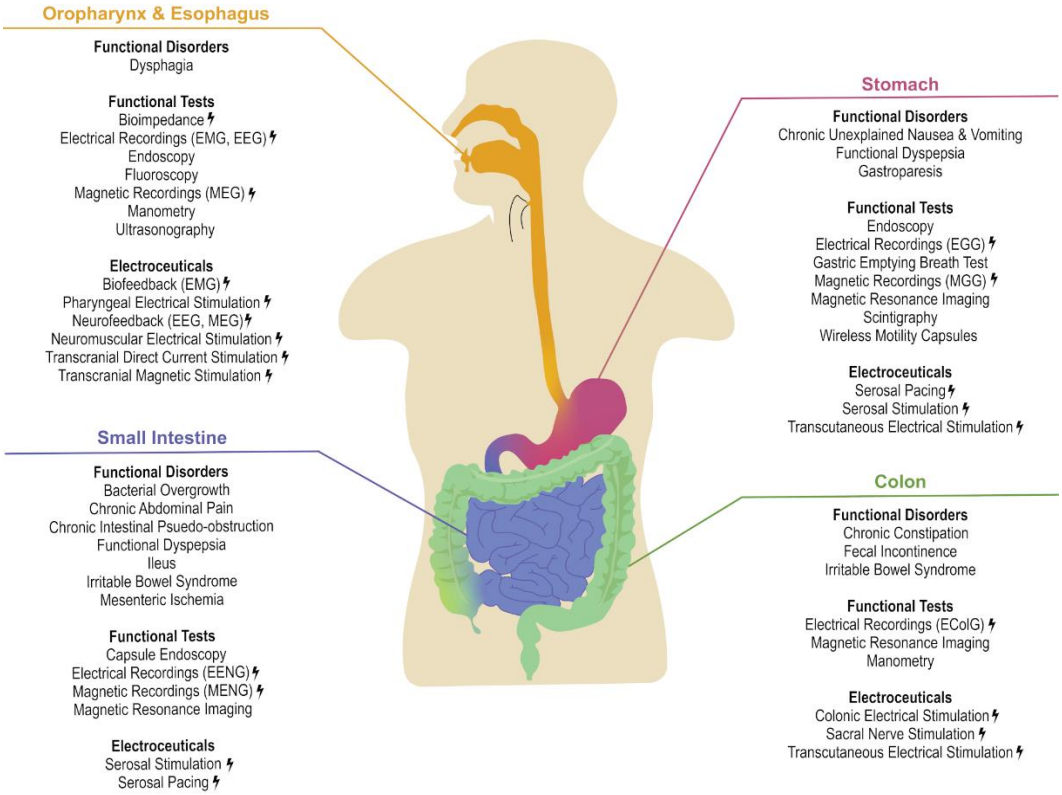

Figure 1. The overview of functional disorders within the gastrointestinal (GI) tract together with conventional motility tests and bioelectromagnetic diagnostic methods and therapies.

The digestive process is reliant on coordinated contractions and motility patterns unique to each organ and its respective function. These motor activities are coordinated by bioelectrical events, sensory and motor nerves, and hormones [2,3]. The patterned pharyngeal response and proximal esophageal contractions can be volitionally modulated, but are mainly regulated by the central and enteric nervous system [3]. In contrast, the motility patterns in the rest of the GI tract are involuntary and coordinated by the enteric nervous system and bioelectrical events known as slow waves (SWs) that are generated by a specialized network of pacemaker cells known as interstitial cells of Cajal (ICC) [4].

Functional GI disorders (FGIDs) are motility problems within the GI organs which do not stem from an anatomical or structural abnormality. In general, the dysfunction is caused by impaired neuromuscular activity where the underlying pathophysiological factors are largely unknown [5]. FGIDs are common, with a recent global-scale study reporting more than 40% of the population have at least one FGID [6]. FGIDs are also reported to result in a direct healthcare cost of USD 5000–8000 annually per patient in the US [7]. Despite their high prevalence rate and impact on the health system, the diagnosis of FGIDs is challenging and remains largely exclusionary. Figure 1 lists the most prevalent FGIDs specific to each GI organ together with current clinical functional tests.

Conventional therapies primarily target symptoms, as the etiologies of many FGIDs have not been completely elucidated. However, there is a substantial research on the brain–gut axis and the bidirectional communication between the enteric nervous system and the central nervous system [8,9]. Bio-behavioral interventions such as cognitive-behavioral tests and heart rate variability biofeedback have shown to be effective in reducing the symptoms of certain FGIDs and enhancing the quality of life [10,11]. These cognitive behavioral-based interventions are hypothesized to target the underlying biopsychological factors of FGIDs and reduce symptoms via autonomic regulation of the GI tract [10]. Another therapeutic approach that has garnered significant interest in the clinical field is the use of electroceuticals.

Electroceuticals is a term for bioelectrical therapies to treat diseases and have recently gained a significant interest. New electroceutical approaches are being investigated for disorders ranging from cardiovascular disease to rheumatoid arthritis and cancer [12]. Similarly, electroceuticals could potentially provide therapeutic benefit to FGIDs, as there is an increasing level of research and clinical evidence suggesting a link between FGIDs and impaired bioelectrical activity [13], and bioelectrical therapy can influence and modify GI tract function [14].

The techniques to measure bioelectrical activity and/or apply bioelectrical therapy differ for each organ (see Figure 1), but they can broadly be categorized in two groups: (i) invasive and (ii) non-invasive methods. Invasive methods utilize electrodes in contact with the surface of organs, which limit their widespread use. However, these methods provide the most accurate results in measurement or treatment. Non-invasive methods utilize electrodes on the body surface or away from the body, meaning techniques can be more widely applied. However, as the electrodes are located away from the target organs, the acquired or applied signals are less well-defined.

This review primarily focuses on the slow wave activity in the GI tract and covers existing techniques for measuring bioelectrical activities from organs in the GI tract (see Table 1) and the bioelectrical signatures of certain disorders that can potentially guide diagnosis. In addition, the review also covers bioelectrical therapies for FGIDs (see Table 2).

2. Oropharynx and Esophagus

Swallowing is a combination of voluntary and reflex actions and involves passing food from the mouth through the pharynx and into the esophagus. Safe swallowing requires precise and complex coordination of both voluntary and involuntary motor activities. Failure to coordinate these activities leads to disturbances in swallowing known as dysphagia. Dysphagia can be a consequence of central and peripheral sensorimotor deficits related to a broad spectrum of diseases, including stroke, neurodegenerative diseases, e.g., Parkinson's, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease, or tissue trauma as a consequence of head and neck cancer [15]. Dysphagia can lead to serious health problems, including respiratory complications, aspiration pneumonia, nutritional compromise, dehydration, reduced quality of life and death [16].

Dysphagia management practices are imprecise, in part due to a limited number of non-specific diagnostic tests and medical therapies. The majority of diagnostic techniques focus on detailing general swallowing biomechanics through visualization modalities such as fluoroscopy, endoscopy, and ultrasonography [17,18]. Without further analysis of the underlying muscle physiology, the primary level of impairment is often unidentified [19]. Pharyngeal and esophageal manometry offers quantifiable investigation of pressure patterns and insights into temporal characteristics that are inadequately captured with visualization modalities. Recently, high-resolution manometry has provided increased spatial resolution [20,21]; however, manometry continues to assess primarily the biomechanics of pharyngeal and esophageal motility.

2.1. Diagnostics

Bioelectrically based methods to investigate swallowing include assessment of either or both central inputs from the cerebral cortex and peripheral inputs at the local oropharyngeal and esophageal musculature [22]. For decades, electromyography (EMG) has been used to investigate the peripheral inputs and activation of musculature involved in swallowing [23]. The intrinsic or extrinsic biopotential of the local musculature results in myoelectric signals that can be measured using either needle-based electromyography (nEMG) or surface electromyography (sEMG). The intramuscular placement of nEMG electrodes into the target tissue allows localized assessment of muscle activity, which was found to have 95% concordance between the acquired signal and muscle activity [24].

Similarly, non-invasive sEMG can identify contraction profiles of muscles during swallowing. A study showed that activity monitored on healthy and stroke patients with three electrodes placed on the perioral, masseter, and infrahyoid muscle provided information on the contraction sequence of

the three selected muscle sites [25]. Moreover, the dysphagia patients compared to healthy controls produced higher and more variable amplitude characteristics (37 vs. 18 mV) over a shorter duration (1.2 vs. 1.9 s) with less coordination when swallowing [25]. More recently, high-resolution sEMG has been utilized to differentiate motor activities across different bolus volumes, bolus viscosities, and head postures [26]. The results have shown that high-resolution sEMG recordings can provide detailed spatial and temporal properties of the muscle electrical activity that can help identify the muscle contractions closely related to swallowing function [26].

Surface electrodes are also used in bioimpedance recordings of swallowing. Applied bilaterally across pharyngeal musculature, current injection and sensing electrodes have been shown to detect the sequential superior or inferior closure of the pharynx in 64% of swallows [27]. Measured concomitantly with pharyngeal manometry, a reasonable correlation was found between bioimpedance and manometric features [27]. A recent study on an ALS patient measured bioimpedance magnitude and phase while simultaneously performing fluoroscopy imaging [28]. The impedance phase and magnitude correlated to the chronological series of anatomical events; however, no significant difference was found between different swallowing tasks, giving no diagnostic advantage of swallowing functionality over the traditional fluoroscopy method.

Swallowing motor control can also be assessed via cortical neural pathways as the initiation of swallowing is voluntary and engages the motor areas of the cerebral cortex. The integrity of the cortical afferent pathway can be assessed by repetitively applying sensory stimulation to swallowing muscles to create sensory-evoked potentials (SEP) which are then measured at the cortex using electroencephalography (EEG). A study on post-stroke dysphagia patients using SEP showed that there was a significant correlation between latency shortening of SEP and severity in dysfunction of biomechanical swallowing events, suggesting that a disrupted pattern of cortical activation to pharyngeal inputs is associated with the stroke severity [29]. Similarly, non-invasive single-pulse transcranial magnetic stimulation (TMS) to evoke a transient muscle evoked potential (MEP) at associated swallowing musculature has revealed the important role of the motor cortex in the regulation of the complex swallowing process [30]. A study showed that unilateral stroke patients with dysphagia had a smaller pharyngeal response than stroke patients with no dysphagia when TMS was applied to intact cortical hemisphere (mean amplitudes of 64 vs. 118 μV), and had similar responses when applied to the affected hemisphere [31]. Pharyngeal motor responses were also shown to correlate with swallowing recovery, where an increased pharyngeal response was observed after 3 months (17 vs. 9 sites) as functional reorganization occurred [32].

Magnetoencephalography (MEG) has also been used to monitor cortical processes during swallowing. Sophisticated analytical techniques such as synthetic aperture magnetometry can further dissociate the cortical contributions of each separable component of swallowing in the sensorimotor sequence and identify the corresponding spatio-temporal characteristics of cortical activity [33]. By utilizing this technique, a study showed that a reduction in swallowing related cortical activation and a disease related shift of hemispheric lateralization were observed in ALS patients with dysphagia compared to healthy controls [34]. These findings have shown how cortical analysis can be used to investigate and monitor the presence of dysphagia and, with refinement, have the quantitative potential to identify dysfunctions at a primary level for greater precision in developing and prescribing therapies.

2.2. Therapies

Historically, pharyngeal swallowing was considered to be largely a medullary driven reflex [35–37]. Early research by Kahrilas et al. in 1988 expanded on this view by describing swallowing as a patterned response, regulated and upheld by complex neurophysiological processes [38]. Increased precision in neuroimaging techniques has led to further models of swallowing motor control that suggest a significant contribution of the cerebral cortex in modulating the pharyngeal response [39,40]. These advances in neurophysiology along with the role of neuroplasticity in adaptive swallowing behavior have led to a shift in dysphagia therapy from compensation to the recovery of swallowing

function. Early approaches to rehabilitation focused on direct changes to muscle recruitment with peripheral strengthening approaches. More recently, rehabilitation approaches have expanded to highlight engagement of cortical regions in the control of motor programming for swallowing [41], employing principles of neural adaptation to rehabilitation approaches [15].

The use of motor imagery of swallowing for dysphagia rehabilitation was first investigated using EEG [42]. Human–computer interfaces have since been created to allow patients to visualize their swallowing function in real time. These interfaces used EEG or MEG to support neurofeedback for sensory activation and EMG, or other measures of swallowing biomechanics, to provide biofeedback for adaptation of peripheral muscle activation [43]. These functional feedback therapeutic techniques increase swallowing muscle strength, correct biomechanical sequencing of swallowing structures and may promote neural plastic changes to reform swallowing neural circuitry pathways [44,45].

Stimulation of the oropharynx and esophagus is challenging due to lack of rhythmic myoelectrical activity and the complexity of biomechanical movements, particularly in the pharynx. Stimulation strategies include pharyngeal electrical stimulation (PES) and neuromuscular electrical stimulation (NMES). A study which performed PES on post-stroke dysphagia patients showed improvements in the sequencing of swallowing events and reduced aspiration [46], while a more recent PES study reported no improvement in dysphagia [47]. An NMES stimulation device for treatment of pharyngeal dysphagia called Vitalstim Plus (DJO Global Inc, Vista, CA, USA) is commercially available. However, the reported outcomes of NMES in the treatment of dysphagia are inconsistent and often contradicting [48,49]. Central nervous system stimulation strategies include transcranial magnetic stimulation and transcranial direct current stimulation [50,51]. A meta-analysis on central nervous system stimulation strategies concluded that no significant improvements in dysphagia were found with the application of direct current stimulation, while subgroup analysis showed a significant improvement in dysphagia when high-frequency magnetic stimulation was applied over contralesional hemispheres [50]. However, a subsequent meta-analysis that controlled for stimulation hemisphere demonstrated that transcranial direct current stimulation resulted in a more robust clinical effect than transcranial magnetic stimulation studies [51].

3. Stomach

Functional gastric disorders, such as gastroparesis, functional dyspepsia and chronic unexplained nausea and vomiting, are linked with impaired motility activities and patterns in the stomach [13]. Endoscopy is a common method for assessment and diagnosis of gastric conditions. However, its use is primarily related to structural evaluation [52]. Once structural abnormalities are excluded, assessment of gastric emptying can be performed using scintigraphy, breath tests, or wireless motility capsules [53].

Gastric emptying scintigraphy involves eating a meal that contains a small amount of radioactive material and monitoring the rate at which this food leaves the stomach over a 2–4 h period [54]. The wireless capsule test involves swallowing a non-digestible pill which can detect an abrupt rise in pH when it leaves the acidic environment of the stomach [55]. Combinations of pH and temperature signatures in different parts of the gastrointestinal tract help to determine the time course of the capsule along its route to egestion. The gastric emptying breath test involves eating a meal containing [^{13}C]-Spirulina platensis that is absorbed after leaving the stomach and then eventually excreted by the lungs as $^{13}CO_2$. As wireless capsule and breath tests involve no radiation, they may be favored, however, they are only able to provide indirect measures of gastric emptying [56]. Moreover, the efficacy and precision of all methods are highly dependent on the disorder and hence designing a methodology tailored for each FGID is essential to obtain reliable results [53]. Magnetic resonance imaging (MRI) is an emerging technique for quantifying gastric volume and emptying by visualizing the stomach and its contents. Studies have shown that gastric volume assessments were reproducible and consistent with intragastric balloons, and emptying scores obtained from MRI were correlated with those of gamma scintigraphy [57]. Even though monitoring gastric emptying by exploiting such techniques

gives insights about gastric dysmotility, the observations do not explain the underlying factors of such impairments.

3.1. Diagnostics

Bioelectrical events such as SWs have a regulatory role in gastric motility. Therefore, the quantification of SWs has potential for the assessment of FGIDs. The first SW recordings were performed by Alvarez [58], and until the 1990s, a limited number of electrodes were employed to measure SWs from the gastric serosa [59,60]. These low-resolution techniques revealed the temporal features of the SW activity and reported that SWs initiate and propagate at a frequency of approximately 3 cycles per minute (cpm) (see Figure 2a). However, they lacked spatial detail and their quantification was primarily limited to frequency-based analysis. As such, they were also unable to determine mechanisms underlying the initiation, maintenance or termination of SW patterns accurately but served as a strong foundation for our current understanding of GI electrophysiology [61].

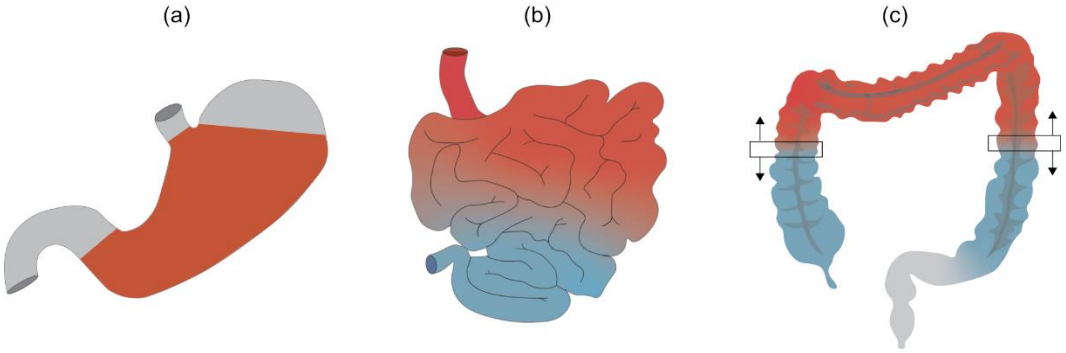

Figure 2. Spatial variation of dominant slow wave (SW) frequencies in the stomach, small intestine, and colon in healthy humans. (**a**) The SW frequency is approximately 3 cpm (red) and uniform across the stomach. (**b**) The small intestine has temporally and spatially dynamic SW patterns where the frequency decreases in a stepwise fashion aborally from approximately 12 cpm (red) in the duodenum to 8 cpm (blue) in the distal ileum. (**c**) Two types of SW rhythms coexist throughout the colon. In the proximal and distal colon, low-frequency activity (2–9 cpm, blue) dominates, while high-frequency activity (9–13 cpm, red) is more prevalent between these regions. The relative size of these zones is variable between subjects.

The introduction of high-resolution SW mapping techniques has overcome such challenges [62]. High-resolution mapping in humans has shown that SWs have varying properties in different regions of the stomach [63,64]. Normal SW activity originates from a pacemaker region on the greater curvature in the upper corpus. Then, the SWs organize into bands and propagate towards and terminate at the pylorus. Abnormal SW activity has been implicated as a disease mechanism in several functional gastric disorders [13]. More importantly, spatially complex SW initiation and conduction patterns that occur within the normal frequency range and cannot be identified using traditional frequency analysis techniques have been linked with gastroparesis and chronic unexplained nausea and vomiting [65,66]. In addition, ICC loss and network degradation have been observed in patients with gastroparesis [67,68]. Therefore, monitoring SW activity is a potential method for diagnosing FGIDs.

Even though high-resolution mapping provides the most accurate SW measures, the invasiveness limits its clinical utility. Therefore, laparoscopic and mucosal mapping approaches have been used to minimize invasiveness. Familoni et al. presented the first laparoscopic extracellular SW recordings from the stomach and small bowel using pairs of stainless-steel electrodes [69]. In the last decade, several approaches were investigated to exploit multielectrode arrays in laparoscopic SW mapping [70,71]. Endoscopic approaches were also investigated as a minimally invasive strategy to measure SWs from the mucosal surface of the stomach [72,73]. Recently, the ability to monitor mucosal SW activity over extended periods has been reported [74].

Reliable methods for non-invasive and possibly long-term recordings of SW activity such as body surface electrogastrography (EGG) would be a significant advance for clinical diagnosis. EGG is a technique to measure gastric myoelectrical activity using electrodes located on the body surface. Several studies have used EGG to assess FGIDs such as gastroparesis, functional dyspepsia and chronic nausea, and observed abnormal EGG patterns [75,76]. Recently, high-resolution electrodes have been employed in EGG measurements to assess the signatures of gastric disorders. The spatial distribution of the electrodes has enabled the characterization of the spatio-temporal patterns of the gastric electrical activity in addition to its frequency dynamics. One study showed that abnormal spatial metrics obtained through high-resolution EGG recordings correlated with the severity symptoms of gastric disorders such as gastroparesis and functional dyspepsia [77].

Magnetogastrography (MGG) is the magnetic counterpart of EGG and is a non-invasive and noncontact alternative [78,79]. MGG provides a higher signal-to-noise ratio (SNR) compared to EGG as magnetic fields are not as greatly attenuated by muscle and fat layers surrounding the body, and hence detects sources located deeper within the body than electrical-based recordings [80]. A recent study showed that extracting SW propagation parameters such as direction and speed from the experimental MGG recordings is feasible [81]. These parameters were altered in diabetic gastroparesis patients where reduced propagation velocities associated with retrograde propagation patterns were reported, while the dominant SW frequency did not show a significant difference [82].

3.2. Therapies

Gastric electrical stimulation has been proposed as an alternative therapy for gastric motility disorders such as gastroparesis and functional dyspepsia. The overall goal for electrical therapy is to improve gastric motility by enhancing contractions, normalizing propagation, or modulating the function of a sphincter. Electrical stimulation is usually performed by using either short pulses at a high-frequency or long pulses at a low-frequency also known as gastric pacing [83].

High-frequency electrical stimulation in the GI tract was first trialed by Bilgutay et al. in 1963 to stimulate the stomach and intestine for the treatment of ileus [84]. Later, it was performed on gastroparesis patients for whom the distal corpus and proximal antrum achieved the most effective stimulation response and resulted in symptom relief and improvements in gastric emptying rates [85]. Subsequently, two other studies have performed stimulation using similar techniques on refractory-diabetic or idiopathic gastroparesis subjects, and have shown that over 70% of the subjects reported improvements in symptoms with reduced nausea and vomiting scores, and that 73% of the subjects experienced an improvement in the quality of life [86,87]. Enterra Therapy (Medtronic plc, Minneapolis, MN, USA), is one form of high-frequency stimulation which utilizes an implantable pulse generator.

The efficacy of Enterra Therapy has been the focus of a number of studies, and two meta-analysis studies reported that high-frequency stimulation significantly improved gastric emptying rates and symptoms [88,89]. However, conflicting findings have been reported by a comprehensive multicenter, randomized controlled trial performed on patients suffering from chronic or refractory vomiting with or without gastroparesis [90]. This study showed that although symptoms were improved (vomiting episodes were reduced in 31% of patients with the stimulation), no observable improvements were reported in gastric emptying rates or quality of life. Enterra Therapy has been shown to not alter or entrain the underlying SW patterns, and the mechanism for symptomatic improvements remains uncertain [91]. It has been proposed that the symptomatic improvements are a result of activation of vagal afferent pathways that influence central nervous system control mechanisms for nausea and vomiting, accompanied by enhanced vagal efferent autonomic function and decreased gastric sensitivity to volume distention [92].

Gastric pacing and transcutaneous electrical stimulation (TES), unlike high-frequency stimulation, have been applied in a relatively limited number of studies. Two studies have shown that gastric pacing was able to entrain the SW activity in the stomach, which resulted in improved symptoms and

accelerated gastric emptying in patients with gastroparesis [93,94]. More recently, spatio-temporal responses of SWs to different pacing parameters that can potentially guide the therapies were studied in porcine models by integrating with high-resolution SW mapping [95,96]. However, the lack of implantable devices that can deliver the energy needed for pacing remains a research challenge. Similarly, only two studies have investigated TES in patients with functional dyspepsia, with a 55% reduction in symptom scores reported in one study [97]. Improved dyspeptic symptoms, quality of life, and gastric emptying were reported in the second study when a wearable stimulation device was used [98]. There is a significant need for more controlled studies to identify optimal parameters to reveal the efficacy of both gastric pacing and TES.

4. Small Intestine

Small intestinal disorders are a frequent cause for a variety of clinical symptoms or pathologies, such as chronic pain, dyspepsia, ischemia, irritable bowel syndrome (IBS), chronic intestinal pseudo-obstruction, bacterial overgrowth, or ileus [99,100]. However, localization of such disorders can be challenging because endoscopically accessing the small intestine is physically difficult as it is over 7 m long in an adult. Therefore, such disorders are often difficult to diagnose and treat. Current techniques for assessment of small intestinal motility include tracing the passage of a food bolus, measuring propagation velocities with manometry, or imaging the frequencies of contractions [100]. However, transit time measures only represent sections of the gut or the entire gut, and do not reveal localized motility patterns. Manometry provides site-dependent quantitative pressure data, thus permitting an indirect quantification of bowel wall motion. However, it requires the uncomfortable insertion of a long catheter under sedation and is rarely performed. Capsule endoscopy is also commonly used to assess and quantify small intestinal function as it can measure the temperature, pH, and pressure of its surrounding environment while it travels passively through the gastrointestinal tract via gut peristalsis before being excreted [55].

Classical imaging techniques such as ultrasound and x-ray fluoroscopy are not well suited to monitor bowel motility because of ionizing radiation, views hampered by intestinal gas, and a lack of reproducibility. MRI is emerging as a promising alternative with advantages including the ability to non-invasively image sections or the entire gastrointestinal tract in multiple planes or three-dimensions [57]. Initial attempts to image small intestine motility using dynamic MRI showed the ability to detect the peristaltic patterns of the gastric antrum and proximal small intestine in fasting and fed subjects and in subjects with pharmacologically stimulated peristalsis [101]. However, as the small intestine has thin walls and is often collapsed, bowel motility can only be visualized reliably when distended and filled with contents that provide sufficient contrast with the walls. Despite these challenges, MRI has been able to reliably extract the frequency of small intestine contractions and changes in intraluminal cross-sectional caliber [100].

4.1. Diagnostics

The slow wave patterns in the small intestine are both temporally and spatially dynamic [102]. This is related to the function of the small intestine to breakdown, mix and absorb the nutrients of the ingested foods. Unique to the small intestine, the slow wave frequency decreases in a stepwise fashion aborally (see Figure 2b) [103]. In humans, the duodenum has a frequency of 12 cpm, and this frequency drops to approximately 8 cpm at the distal ileum [104]. In the small intestine, contractions of the muscle are also associated with spiking activity or action potentials occurring in conjunction with the slow waves [102].

Although rarely used due to their invasiveness, one of the most reliable methods for the measurement of the small intestinal electrical activity is the use of serosal or intraluminal electrodes. Serosal electrodes can be implanted on the serosal surface of the small intestine [104,105], whereas intraluminal electrodes can be placed under endoscopy [106,107]. The reliable assessment of SW

signals in the small intestine is complicated, as the signals are extremely weak compared to background noise and other biological signals (such as the heart or even the stomach).

Despite the weak nature of these signals, a number of groups have reported success at non-invasively detecting the resultant activity on the skin surface using electroenterography (EENG) [108,109]. Another study has also reported the ability to non-invasively detect increased spike burst activity in the presence of higher levels of bowel contractions [110]. However, such techniques rely on sophisticated filtering methods and electrode platforms to overcome the low SNR of the EENG signals [111]. Most likely, such techniques work best on subjects with low body mass index due to the insulating effects of the fat layers [112].

An alternative approach involves non-invasively detecting the resultant magnetic fields using magnetoenterography (MENG). Richards et al. were among the first to report the ability to non-invasively and spatially map the biomagnetic activity from the different regions of the normal human small intestine [79]. Subsequently, MENG signatures from chronic mesenteric ischemia patients have been reported [113]. In that study, MENG recordings were obtained pre- and post-revascularization surgery on chronic mesenteric ischemia patients. Prior to revascularization surgery, MENG recordings reported a significant decrease in slow wave frequency post-prandially (8.9 vs. 7.4 cpm). Post-surgery MENG recordings reported consistent slow wave frequencies before and after the food was ingested (9.3 vs. 9.4 cpm).

4.2. Therapies

As mentioned in Section 3.2, the earliest reported study on gastrointestinal electrical stimulation focused on treating post-operative ileus [84]. That study stimulated the stomach and the duodenum and attempted to determine locations where the most effective peristalsis response was obtained. Since that initial study, there have been limited human studies employing electrical stimulation or pacing in the small intestine [114]. However, there have been a number of animal studies that have attempted to either accelerate or decrease intestinal transit by altering the motility patterns. Decreasing transit times can help to increase absorption (for example, to treat short gut syndrome) [115,116] or to treat obesity by delaying gastric emptying and prolonging satiety [117]. Although SW entrainment and functional changes have been achieved in a number of animal studies, limited success has been observed in one human study reported to date [114].

5. Large Intestine

Functional bowel disorders (FBD), such as IBS, chronic constipation, and fecal incontinence (FI), affect almost half of the population [118]. Despite the high prevalence rates, the diagnosis of FBDs mostly relies on subjective assessments such as clinical history, physical examination, and regular follow-up. Colonic motor activity is difficult to monitor and evaluate because of its erratic nature and the inaccessibility of the colon. In recent years, the use of MRI and high-resolution manometry to assess colonic motility has become more common. MRI has been used to measure the whole gut or colon transit time by tracing meals or markers [119]. In addition, several studies have shown the feasibility of assessing colonic motor patterns using MRI by employing visual assessments of wall motility, observing or quantifying the changes in the luminal diameter over time, and mapping the motility of the contents [120]. However, such techniques usually require bowel preparation and are prone to yield errors due to non-standardized methods. By measuring the pressures along the colon, high-resolution manometry has been shown to be useful to more accurately monitor the prominent motor patterns in the colon [121]. The improved resolution of recording sites helps to identify propagating motor patterns that are mostly missed by low-resolution manometry recordings. However, manometry performed via intubation of a catheter is an invasive procedure and, in most institutions, involves some form of anesthesia. Both MRI and manometry can provide insights on functional bowel symptoms and diseases by monitoring motor patterns, but the underlying factors still need to be identified.

5.1. Diagnostics

Bioelectrical measurements to assess the functionality of the large intestine were first used more than 50 years ago [122]. Several techniques, such as serosal, intraluminal, and cutaneous electrical measurements, have since been utilized. However, SW activity within the colon is less well-defined and more variable compared to the stomach and intestine which has led to conflicting reports [123]. Moreover, the temporal and spatial profiles of colonic electrical activity have shown to be variable between people [124]. In general, two types of SW rhythms coexist throughout the colon: (i) a high-frequency activity with low amplitude (9–13 cpm) and (ii) a low-frequency activity with high amplitude (2–9 cpm) [123–125]. The low-frequency activity was more dominant in the proximal and distal colon, while the high-frequency activity was more dominant between these zones (see Figure 2c). The extent of these dominant zones was reported to be highly variable between subjects [124].

The first non-invasive measurements of colonic SW also known as electrocolonography (EColG) was reported by Taylor et al. in 1975 [125]. Pezzolla et al. performed transcutaneous electrical recording on the patients who underwent colectomy and reported that the power peaks between 3.5 and 7.5 cpm were observed before colectomy but were not present after [126]. More recently, high-resolution cutaneous electrodes were introduced to analyze changes in colon motor activity in humans during a meal-response study [127]. In the study, a 32-channel electrode array was utilized and roughly 3 h recordings with pre- and post-meal epochs were performed. A SW activity with a dominant frequency of 4 cpm was reported in the sigmoid colon region in agreement with earlier invasive studies.

Several studies have attempted to identify the relationship between FBDs and underlying SW activity using myoelectrical recordings. A study performed on patients diagnosed with IBS reported that the low-frequency band of SW was recorded for a greater proportion of time in both the rectum and rectosigmoid compared to normal subjects [128]. A subsequent study showed that the frequency of colonic contractions was closely associated with the underlying SW frequency [129]. However, no differences were observed in the relationship between contractions and SW frequency between IBS and control groups. On the other hand, a couple of subsequent studies [130,131] failed to reveal the preponderance of low-frequency band of SW activity in patients with IBS as previously reported [128].

Bioelectrical signatures of constipation and diarrhea have been the focus of several studies as well. Bueno et al. performed measurements from the mucosal surface of patients with constipation and diarrhea [132]. The findings were consistent with earlier studies and reported the existence of low-frequency and high-frequency SW rhythms in the colon. In addition, spike bursts of either short or long duration were reported. Constipation patients had a 2–4-fold increase in the number of short duration spike bursts compared to controls, whereas diarrhea patients had an absence of short duration spike bursts and a reduction of the number of long duration spike bursts (3–8 vs. 20–26 spike bursts per hour) [132]. In a similar study performed on constipation patients, meal ingestion resulted in a moderate increase in spike bursts, whereas a prompt and significant increase was observed in healthy subjects [133]. In addition, SW activity was also reported to be impaired in patients with constipation, with no SWs recorded from the entire colon in more than half of the constipation patients, and weak activity was observed in the right colon in the rest of the patients [134]. Such impaired SW activity may be related to a deficit of ICC in the colon of patients with constipation [135].

5.2. Therapies

A number of electrical therapy methods, such as sacral nerve stimulation (SNS), colonic electrical stimulation (CES), and TES, have been introduced for treating FBDs such as FI and constipation. SNS is performed with a stimulator and electrodes implanted on sacral nerves 2–4 which provide continuous stimulation to the nerve. SNS implants were initially introduced to the market by Medtronic as InterStim, and since then, Axonics Modulation Technologies Inc (Irvine, CA, USA) have developed smaller and rechargeable implants [136]. SNS has been trialed in a number of studies to improve symptoms and quality of life in constipation, but the evidence that SNS is effective for constipation is limited [137,138]. On the other hand, several controlled studies have shown that the objective and

subjective measures, functional outcomes and quality of life for FI patients improved significantly with SNS compared to controls. In addition, a significant reduction in weekly incontinence episodes and incontinence scores was observed, while the ability to defer defecation was increased [139,140]. The clinical outcomes suggest that SNS can be a safe and effective alternative treatment for FI patients, but adverse events and cost are still an important factor in practice.

Since the SW activity pattern along the colon is non-uniform, electrical stimulation or pacing is difficult to design and execute. A limited number of animal studies have trialed CES to improve colonic contractions and motility patterns, and reported that CES accelerated colonic transit and induced colonic contractions [141,142]. Similarly, TES was applied to patients with constipation, and it was reported that there was a significant improvement in the quality of life, colonic transit time and laxative use [143,144]. However, more controlled studies are required to confirm the efficacy of both CES and TES.

6. Summary and Future Directions

Since Walter Alvarez's first electrical recordings of the GI tract almost 100 years ago, the bioelectrical signatures of the GI organs have been extensively studied and identified [58]. However, there remains much to explore in the pursuit of bioelectrically based diagnostic tools and therapies for FGIDs. Advances in high-resolution mapping techniques in the last three decades have provided deeper insights into the GI electrophysiology and pathophysiology [145]. Existing research shows a clear relation between certain FGIDs and impaired bioelectrical activity (see summary in Table 1). In parallel, the discovery of ICC and their function in GI motility has helped to identify the underlying factors of certain FGIDs and has become a major research focus [67]. Such advances and findings in the GI electrophysiology have shown that assessment of bioelectrical activities could potentially help to identify the diverse etiologies of FGIDs and overcome the drawbacks of the current clinically adapted methods, which mostly target symptoms and are often unreliable and exclusionary. However, the lack of more accurate and reliable but less invasive methods remains a significant challenge for clinical translation of bioelectrical assessment of the GI tract.

Table 1. The techniques to measure the bioelectrical activity along the GI tract.

Technique	Organs	Advantages	Limitations
Low-resolution serosal recordings	Stomach [58–60] Small intestine [103,104] Colon [122,124,125,134]	High SNR Suitable for long term recordings	Invasive No spatial information
High-resolution serosal recordings	Stomach [63–66] Small intestine [105]	High SNR Spatial information	Invasive Expensive equipment
Laparoscopic serosal recordings	Stomach [69–71] Small intestine [69]	High SNR Reduced invasiveness	Limited coverage
Mucosal/intraluminal recordings	Stomach [72–74] Small intestine [106,107] Colon [122,125,128–133]	Minimally invasive	Low SNR
Cutaneous electrical recordings	Oropharynx and Esophagus (sEMG [25,26], EEG [29–32]) Stomach (EGG) [75–77] Small intestine (EENG) [108–110] Colon (EColG) [125–127]	Non-invasive Suitable for long term recordings Cheap and portable equipment	Low SNR Indirect measurement
Cutaneous magnetic recordings	Oropharynx and Esophagus (MEG) [33,34] Stomach (MGG) [78–82] Small intestine (MENG) [79,113]	Non-invasive Non-contact Higher SNR than cutaneous electrical recordings	Large and expensive equipment Indirect measurement

Similarly, electroceuticals have also gained significant interest from researchers (see summary in Table 2). Recently, the National Institutes of Health have initiated an ambitious research program entitled the Stimulating Peripheral Activity to Relieve Conditions (SPARC, https://sparc.science/) to transform

our understanding of nerve–organ interactions with the intent of advancing bioelectronic medicine. Studies have reported promising outcomes in terms of improvement of the symptoms of FGIDs, suggesting that electroceuticals which directly target the underlying conditions could potentially be an effective therapy in the treatment of FGIDs, and replace the limited existing conventional methods [14]. However, more reliable, long-term and randomized human clinical trials targeting all GI organs are needed to prove the efficacy of electrical therapies, as there is insufficient evidence of efficacy from the limited number of human studies.

Table 2. Bioelectrical therapies for functional gastrointestinal disorders (FGIDs).

Technique	Target Organs	Description	Therapeutic Targets
Serosal pacing	Stomach [93–96]	Low-frequency, high-energy direct stimulation	Gastroparesis
Serosal stimulation	Stomach [84–90] Small intestine [84,114–117] Colon [141,142]	High-frequency, direct stimulation	Gastroparesis Chronic unexplained nausea and vomiting
Transcutaneous electrical stimulation	Stomach [97,98] Colon [143,144]	High-frequency, indirect stimulation	Functional dyspepsia Chronic constipation Fecal incontinence Irritable bowel syndrome
Sacral nerve stimulation	Colon [136–140]	High-frequency, nerve stimulation	Chronic constipation Fecal incontinence Irritable bowel syndrome
Biofeedback/Neurofeedback	Oropharynx and Esophagus (EMG, EEG, MEG) [42–45]	Classification of muscular/neural activity for functional feedback	Dysphagia
Pharyngeal electrical stimulation	Oropharynx and Esophagus [46,47]	High-frequency, direct stimulation	Dysphagia
Neuromuscular electrical stimulation	Oropharynx and Esophagus [48,49]	High-frequency, direct or indirect stimulation	Dysphagia
Transcranial (direct current or magnetic) stimulation	Oropharynx and Esophagus [50,51]	High- and low-frequency stimulation to the brain	Dysphagia

In order to advance clinical translation of bio-electrical methods of investigation and therapeutics for FGIDs, there needs to be a concerted effort to transition from treating the symptoms to addressing the underlying causes. Moreover, a closed-loop stimulation or pacing system that is operated by the inputs from the different mechanisms modulating the gut motility could potentially increase the efficacy of bioelectrically based therapies. However, such system requires the ability of performing long-term recordings and developing sophisticated real-time analytical methods. Recent advances in technology, such as cloud and edge computing, miniaturization of devices, and light-fidelity communication, could be incorporated to achieve personalized therapies.

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Abbreviations

ALS	Amyotrophic Lateral Sclerosis
CES	Colonic electrical stimulation
cpm	Cycles per minute
EColG	Electrocolonography
EEG	Electroencephalography
EENG	Electroenterography
EMG	Electromyography
EGG	Electrogastrography
FBD	Functional bowel disease
FGID	Functional gastrointestinal disorder
FI	Fecal incontinence
GI	Gastrointestinal
ICC	Interstitial cells of Cajal
IBS	Irritable bowel syndrome
MEG	Magnetoencephalography
MENG	Magnetoenterography
MEP	Muscle evoked potential
MGG	Magnetogastrography
MRI	Magnetic resonance imaging
NMES	Neuromuscular electrical stimulation
PES	Pharyngeal electrical stimulation
SEP	Sensory evoked potential
SNS	Sacral nerve stimulation
SW	Slow wave
TES	Transcutaneous electrical stimulation
TMS	Transcranial magnetic stimulation

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