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Emerging noninvasive neuromodulation methods for functional gastrointestinal diseases

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INTRODUCTION

Functional gastrointestinal diseases (FGIDs) are the most prevalent disorders of the gastrointestinal tract that extends from the esophagus to the anus, which include gastroesophageal diseases (GERD), noncardiac chest pain, swallowing disorders, functional dyspepsia (FD), gastroparesis, functional abdominal pain, intestinal pseudo-obstruction, irritable bowel syndrome (IBS), postoperative ileus, constipation and diarrhea, pelvic pain, and others.[1] Due to the functional nature of disorders and lack of biomarkers, the diagnosis is largely based on symptoms.[2]

Pathophysiology of FGIDs is largely unknown. However, visceral hypersensitivity, gastrointestinal dysmotility, and disorders of the brain-gut interaction are believed to play major roles in most of FGIDs, such as FD, IBS, and abdominal pain. Due to limited pathophysiological understanding and heterogeneity of the diseases, treatment options are very limited for most of FGIDs and most of the available therapies are symptom based and often controversial. For example, abdominal pain and dysmotility are two hallmark symptoms of IBS; analgesics and medical neuromodulators (antidepressants) are commonly used for treating abdominal pain. However, the use of these medications leads to worsening of intestinal dysmotility. Another example is the use of prokinetic agents for treating delayed emptying of the stomach for gastroparesis (defined as delayed gastric emptying of solids). Although it is a pathophysiological choice for improving gastroparesis, it reduces gastric accommodation and worsens other symptoms of gastroparesis, such as early satiety and fullness (due to impaired fundic relaxation and reduced ability to accommodate ingested food).

Recently, FGIDs are considered as disorders of the brain-gut axis, and autonomic dysfunction has been frequently reported in FGIDs.[3] The autonomic nervous system (ANS), composed of sympathetic and parasympathetic nerves, is known to play an important role in the brain-gut interaction. The afferent nerves of the ANS carry signals from a gut organ to the brain and the efferent nerves convey reflexive signals from the brain to the gut organ in response to the event in the organ. For example, once the stomach is ingested with a meal, the vagal afferent carries a signal to the brain and the brain sends an enhanced vagal efferent activity that results in release of nitric oxide in the fundus, causing fundic relaxation to accommodate ingested food; meanwhile, the enhanced vagal efferent activity stimulates release of acetylcholine in the antrum, causing antral contractions to empty the ingested food. In a diseased state, this vago-vagal reflex may be compromised and one or all of the following might happen: (1) the vagus nerve is not able to send the right afferent signal to the brain; (2) the ability of the brain to process the afferent signal is impaired; and (3) the vagus efferent cannot be appropriately activated. While current technologies are limited in and/or incapable of assessing afferent signals from the gut to the brain, numerous studies have reported impaired processing or altered brain functions and impaired

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autonomic functions in patients with FGIDs or animal models of FGIDs.[4]

Hypothetically, neuromodulation (modulation of neural activity) can be used to treat disorders of the brain-gut interaction. It may be used to send an appropriate afferent signal to the brain when something goes wrong in a gut organ, a method called afferent stimulation. It can also be used to directly enhance the efferent activity, a method called efferent stimulation. The afferent neuromodulation may also be used to improve the brain functions associated with disorders of a gut organ.

Neuromodulation can be accomplished directly by electrical stimulation or indirectly by other means such as magnetic stimulation, ultrasound stimulation, and light stimulation, as well as manual acupuncture and electroacupuncture. Electrical neuromodulation can be classified as follows: direct nerve stimulation, such as vagal nerve stimulation, sacral nerve stimulation, spinal cord stimulation, and deep brain stimulation, and indirect nerve stimulation, such as transcutaneous auricular vagal nerve stimulation (taVNS), transcutaneous cervical vagus nerve stimulation (tcVNS), transcutaneous electrical acustimulation (TEA), transabdominal interferential stimulation, and transcutaneous tibial nerve stimulation (tTNS).

Noninvasive neuromodulation has at least one of the following two distinct features: (1) it stimulates a nerve or nerves that are superficial or underneath the skin or (2) it delivers electrical stimulus that is capable of penetrating the skin to reach a nerve or nerves. Unless the nerve being stimulated *via* a noninvasive neuromodulation method is directly innervated with the targeted organ, which is rare, noninvasive neuromodulation is considered as an afferent stimulation, that is, it sends an appreciate signal to the brain and enables the brain to send corrective efferent signal to the diseased organ. In the following section, we will discuss the perspectives of a few emerging noninvasive neuromodulation methods and their applications in treating FGIDs.

NONINVASIVE NEUROMODULATION FOR FGIDS

Various methods of noninvasive neuromodulation have been applied for treating FGIDs. In this perspective, we will only discuss emerging methods (excluding transcutaneous electrical nerve stimulation and electroacupuncture) and classify them based on stimulation locations such as auricular vagus nerve, cervical vagus nerve, acupuncture points, transabdominal stimulation, and tibial nerve. Table 1 presents a summary and comparison of these methods.

Auricular vagal nerve stimulation

The ear is innervated with the vagal afferent nerve, and the auricular concha is most densely innervated with the vagal afferent.[5] Due to its shallowness underneath the skin, the auricular vagus nerve is an ideal targe for noninvasive stimulation. Two methods have been applied for treating FGIDs: taVNS and percutaneous auricular vagal nerve stimulation (paVNS).

taVNS is accomplished *via* surface electrodes or clipper electrodes placed at an area where the auricular vagus nerve is innervated, most commonly in the symba concha. pcVNS is delivered *via* small and short (a few millimeter) needles penetrated through the skin. Both taVNS and pcVNS use low-frequency stimulation ranging from 2 Hz to 100 Hz.

Due to direct projection of the auricular vagus nerve to the nucleus tractus solitarius, taVNS has been used for treating neurological disorders such as migraine, epilepsy, depression, tinnitus, and other clinical conditions.[6] However, recently, taVNS has been applied for treating patients with FD and IBS. In one randomized clinical trial (RCT) study, taVNS was shown to improve symptoms of dyspepsia, and anxiety and depression in 36 patients with FD.[7] Physiologically, it improved gastric accommodation and pace-making activity by enhancing vagal efferent activity. The concurrent improvement in gastric accommodation and gastric pace-making activity is most interesting and represents a unique feature of taVNS. The improvement in gastric accommodation is believed to be attributed to the vagally mediated release of nitric oxide in the fundus, whereas the enhancement of pace-making activity is attributed to the vagally mediated release of acetylcholine. In another single-center RCT study, taVNS was reported to improve overall symptoms of IBS, abdominal pain, and constipation in 42 patients with constipation-dominant IBS.[8] The concurrent improvement in pain and constipation is another distinct advantage of neuromodulation, which is rarely observed with medical therapy. Most often, medical analgesics worsen constipation. The other interesting finding of the study was the improvement in rectal sensory functions: the sensation threshold to rectal distention was decreased after taVNS. The improved rectal sensation to rectal distention is believed to play a role in the improvement of constipation, as rectal hyposensitivity is one of the pathophysiological factors of constipation. As the rectum is not innervated with the vagus nerve, the ameliorating effect of taVNS on the rectal sensory function was hypothesized to be attributed to vagal afferent and sacral efferent pathway. These findings suggest that taVNS may alter gastrointestinal functions mediated by not only the vago-vagal pathway but also the vago-sacral pathway.

Table 1: Comparisons among different methods of noninvasive neuromodulation

Stimulation method	Stimulation location	Stimulation frequency	Diseases being treated	Advantages	Disadvantages
taVNS[6–8]	Auricular vagus nerve *via* surface electrodes	1–100 Hz	FD, IBS	Self-administered; home based	Daily placement of electrodes
paVNS[9–11]	Auricular vagus nerve *via* needles	1–100 Hz	Pediatric abdominal pain, IBS	Device attached to the ear	Needle penetration; long stimulation duration
tcVNS[12–13]	Cervical vagus nerve *via* surface electrodes	5 kHz	Gastroparesis	Short study duration (a few minutes)	Hand-held device; lack of controlled data
TEA[15–20]	Acupuncture points near the peripheral nerves	1–100 Hz	GERD, FD, gastroparesis, constipation, IBS	Self-administered; home based	Daily placement of electrodes
TIS[21–22]	Various abdominal areas targeting a diseased organ	> 1000 Hz	Pediatric constipation	Noninvasive	Two abdominal stimulation locations need to be well aligned
TNS[23]	Tibial nerve above the ankle	1–100 Hz	Constipation; fecal incontinence	Well-established method; numerous clinical trials	Controversial findings regarding its efficacy

taVNS: transcutaneous auricular vagal nerve stimulation; paVNS: percutaneous auricular vagal nerve stimulation; tcVNS: transcutaneous cervical nerve stimulation; TEA: transcutaneous electrical acustimulation; TIS: transcutaneous interference stimulation; TNS: tibial nerve stimulation; FD: functional dyspepsia; IBS: irritable bowel syndrome; GERD: gastroesophageal diseases.

It is unclear whether the therapeutic effect of taVNS sustains after the termination of the treatment, as no follow-up information was provided in either of the studies. Mechanistically, taVNS was reported to enhance parasympathetic activity. The safety profile of taVNS is excellent as none of these studies reported side effects.

paVNS *via* 2 mm needle electrodes was reported to improve abdominal pain in adolescents with FGIDs (60 patients with active treatment and 55 with sham treatment),[9] resting and evoked pain in 20 adolescents with functional abdominal pain disorders,[10] and symptoms of IBS in 50 adolescents with IBS.[11] In these studies, the therapy was delivered as follows. The ear was transilluminated to visualize the neurovascular bundles, and the electrode wires were placed adjacent to vascular branches of the outer ears and secured with adhesives. The device (attached to the back of the ear) delivered 3.2 V with a rectangular pulse wave and alternating frequencies (1-ms pulses of 1 Hz and 10 Hz) every 2 s, continuously cycling 2 h on and 2 h off for a total of 120 h (5 days). After 5 days, subjects removed the device in the home setting. Subjects thus received active or sham stimulation for 5 days/week with 2 days off each week for a total of 4 weeks. Patients returned to the Translational Research Unit weekly to receive repeat device placements. No significant side effects were reported in any of these studies. In one study,[9] some minor side effects were reported, including ear discomfort (n = 6, three in each arm), adhesive allergy (n = 3, one in active and one in sham treatment), and syncope due to needle phobia (one in sham treatment). Potential mechanisms or possible sustained duration involved in the therapeutic effect of paVNS was not reported.

tcVNS

Typically, aVNS uses low stimulation frequency (≤ 100 Hz) since the auricular vagus nerve is right underneath the skin. tcVNS has to use a high stimulation frequency (5 kHz) in order for electrical current to penetrate the skin down deep to the nerve. In two open-label clinical studies, tcVNS *via* a hand-held device was shown to improve major symptoms of gastroparesis in 35 patients with drug-refractory gastroparesis[12] and 17 patients with diabetic gastroparesis.[13] No serious adverse events were reported. Acceleration in gastric emptying was reported in one study. RCTs are needed to exclude potential placebo effects that are commonly observed in medication therapies in patients with FGIDs including gastroparesis. In addition, mechanistic studies are also needed to determine whether tcVNS enhances vagal activity or improves autonomic dysfunction.

TEA

TEA refers to a method of electrical neuromodulation *via* surface electrodes placed at selected acupuncture points that are in the vicinity of peripheral nerve. The distinct feature of TEA is the use of specific parameters that improve autonomic dysfunction and/or pathophysiology of a targeting disorder, such as dysmotility (25 Hz, 0.5 ms, and 40% duty cycle), visceral hypersensitivity (100 Hz, 0.3–0.5 ms, 20% duty cycle), and/or low-grade inflammation (5 Hz, 0.5 ms, and 10% duty cycle).[14]

Various single-center RCTs have demonstrated the ameliorating effects of TEA delivered *via* surface electrodes placed over acupuncture points ST36 (Zusanli, below kneecap, in the vicinity of peroneal, tibial, and sciatic

nerves) and/or PC6 (Nanguan point on the wrist, over the medial nerve) with specific settings of parameters for GERD, FD, IBS, constipation, and postoperative recovery.[15–19] Mechanistically, TEA is programmed to enhance vagal efferent activity; the enhancement in vagal efferent activity leads to improvement in gastrointestinal motility and inhibition of abdominal pain by suppressing low-grade inflammation *via* the cholinergic anti-inflammatory pathway. That is, TEA at ST36/PC6 enhances vagal efferent activity, resulting in the release of acetylcholine in the gastrointestinal tissue. The release of tissue acetylcholine improves gastrointestinal motility and suppresses low-grade inflammation *via* alpha-7 nicotinic acetylcholine receptor, resulting in improvement of dysmotility symptom and abdominal pain (low-grade inflammation is known to play a major role in abdominal pain), respectively. Concurrent improvement in both abdominal pain and gastrointestinal dysmotility was noted with TEA at acupuncture points ST36 and PC6 in patients with constipation-dominant IBS and patients after abdominal surgery. Integrative effects on the pathophysiology of FGIDs are commonly observed with TEA. In patients with GERD, TEA was found to increase lower esophageal sphincter pressure, distal esophageal peristalsis, and gastric accommodation.[15] A recent TEA study in patients with constipation-dominant IBS reported a sustained anti-constipation effect 5 months after the termination of 4-week daily therapy.[20] No significant side effects were reported in any of the studies. Minor allergic reaction to adhesive electrodes was noted in some patients with TEA.

Transabdominal interference stimulation

In this method, two-channel differential high-frequency (such as 4000 Hz and 4080 Hz) stimulation is delivered transabdominally from two different angles. At the convergent point (the targeting organ), the stimulation currents interfere with each other, resulting in a stimulation at a differential frequency, that is, the difference between two independent stimulation frequencies (4080 Hz – 4000 Hz = 80 Hz). The high-frequency stimulation allows the stimulation current to penetrate through the abdominal wall to reach the targeted organ, and the resulting differential low frequency produces therapeutic effects. This method has been shown to improve constipation and colon motility in pediatric patients with slow transit constipation.[21] It remains to be seen whether this method has a therapeutic potential for treating adult patients with chronic and functional constipation.

TNS

The tibial nerve above the ankle is shallow underneath the skin, and therefore is a good target for noninvasive neuromodulation, including tTNS *via* surface electrodes and percutaneous tibial nerve stimulation (pTNS) *via* needles inserted from the skin. Due to its anatomical connection with the sacral nerve that innervates the colorectum, tTNS and pTNS have been investigated for treating functional constipaiton and fecal incontinence. These methods have been well established and applied in numerous clinical trials. However, controversial results have been reported regarding their effects on constipation and fecal incontinence and there is a lack of well-controlled RCTs.[22] A recent placebo-controlled study reported that sham stimulation was equally effective in treating fecal incontinent, demonstrating the importance of investigating potential sham effects.[23] Similar to other noninvasive neuromodulation methods, TNS has an excellent safety profile with no serious side effects reported in the literature.

FUTURE DIRECTIONS AND CONCLUSIONS

FGIDs are common with limited effective therapies. Therefore, noninvasive neuromodulation is an attractive method for treating FGIDs. Traditionally, noninvasive neuromodulation (same for invasive neuromodulation) is developed for treating functional disorders of an organ or organs that are anatomically connected with the nerve being stimulated, such as the use of taVNS for epilepsy and tTNS for constipation and fecal incontinence. However, recent studies have shown the cross-branch effects of autonomic neuromodulation, such as the effect of taVNS on rectal function[8] and the effects of sacral nerve stimulation on motility functions of the stomach and small intestine.[24] Accordingly, neuromodulation may also be used to treat disorders of organs that are not anatomically connected with the nerve that is being stimulated. For example, vagal nerve stimulation may be used to treat disorders of organs that are innervated with the sacral nerve and sacral nerve stimulation may be applied to treat diseases of organs that are innervated with the vagus nerve.

Further development and research are needed to bring more noninvasive neuromodulation therapies from bench to bedside. Methodologically, optimization of stimulation parameters and treatment regimens is highly recommended. For efferent stimulation, the stimulation parameters should be chosen to enhance parasympathetic activity. For afferent stimulation, the stimulation parameters should be chosen to inform the brain the nature and location of the disorders, which may benefit from the assessment of the endogenous afferent signal associated with the disorder to be treated. Technologically, advanced wearable devices need to be developed preferably with following features: (1) they should be easy to wear and use, such as having a small size and being wireless (electrodes are imbedded with

the stimulators); (2) they should resemble entertainment gadgets, so that the treatment can be delivered in public; (3) they should automatically track adherence to the treatment. Clinically, more RCTs, especially multicenter RCTs, are needed to demonstrate the efficacy of the proposed therapy. Scientifically, more basic research is needed to explore the mechanisms of action involved with noninvasive neuromodulation for FGIDs.

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Conflict of Interest

Jiande DZ Chen is an editorial board member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

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