Parasympathetic Control of Gastrointestinal Motility and Cross-branch Actions of Parasympathetic Neuromodulation

Short running title: Parasympathetic control of GI motility

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Parasympathetic nerve system, composed of the vagus nerve and the sacral nerve, is known to regulate motility of the entire gastrointestinal tract via its direct innervation. Electrical stimulation or neuromodulation of the parasympathetic nerves has been reported to improve gastrointestinal dysmotility that is one of major disorders associated with functional gastrointestinal diseases. Accordingly, this mini review focuses on therapeutic potentials of parasympathetic neuromodulation on gastrointestinal dysmotility and functional gastrointestinal diseases.

In the first part of the review, we summarized available methods of vagal nerve stimulation (VNS) and their applications for treating functional gastrointestinal diseases, including functional dyspepsia, gastroparesis and irritable bowel syndrome. Two noninvasive VNS methods are introduced, including transcutaneous auricular VNS and transcutaneous cervical VNS.

The second part of the review is devoted to sacral nerve stimulation (SNS) and its applications for treating functional gastrointestinal diseases associated with the pelvic organs that are innervated with the sacral nerve, including fecal incontinence, constipation and irritable bowel syndrome. In addition, the potential of SNS for treating dysmotility of the stomach and small intestine that are not innervated with the sacral nerve is also introduced.

A brief perspective is provided on challenges and applications of neuromodulation of the parasympathetic nerves for functional gastrointestinal diseases.

The gastrointestinal (GI) tract is a unique organ that has its own nervous system called enteric nervous system (ENS) and also termed “little brain”. The ENS has 200-600 million neurons and can function independently without inputs from the brain (1). It communicates with the brain via

the autonomic nervous system that is composed of sympathetic and parasympathetic nervous systems. The parasympathetic system consists of the vagus nerve and the sacral nerve.

The vagus nerve, also called the tenth cranial nerve, includes axons which emerge from or converge onto 4 nuclei of the medulla: the nucleus tractus solitarius (NTS), dorsal motor nucleus of vagus nerve (DMV), nucleus ambiguus and spinal trigeminal nucleus. It innervates the gastrointestinal tract from the esophagus to the mid-colon (2). The number of neurons that project to is much less in the transverse and descending colon, compared to the ascending colon (3)

The sacral nerves are the five pairs of spinal nerves that exit the sacrum and innervate pelvic organs, including colon, anorectum, bladder and genital organs (4). In replacing the vagus nerve, the sacral nerve controls the functions of the distal colon, rectum and the anus (3).

Both vagus and sacral nerves are composed of afferent and efferent nerves. The afferent nerves send sensory signals, such as distention, nutrients and pain, to the brain and the efferent nerves carry control signals from the brain to various organs of the GI tract. The parasympathetic control of GI motility is accomplished via various neurotransmitters, such as acetylcholine, substance P, nitric oxide and vasoactive intestinal peptide (5). Activation of parasympathetic nerves and release of acetylcholine result in enhancement of GI motility; whereas activation of parasympathetic nerves and release of nitric oxide lead to inhibition of GI motility. That is, the activation of the parasympathetic nerves may result in both enhancement and inhibition of GI motility, depending on the release of neurotransmitters and density of corresponding receptors.

The vago-vagal reflex is a typical example of the endogenous control of GI motility by the vagus nerve. For example, once the stomach is ingested with foods, the vagal afferent is activated and sends a signal to the brain via the NTS; the brain processes the afferent signal and produces enhanced vagal efferent activity carried to the stomach, results in releases of neurotransmitters; the release of acetylcholine in the antrum induces antral contractions for mixing, grinding and emptying the ingested food; on the other hand, the release of nitric oxide in the fundus relaxes the fundus to accommodate the ingested food.

In addition to the above-mentioned endogenous parasympathetic controls, GI motility can also be controlled or altered exogenously via vagal nerve stimulation (VNS) or sacral nerve stimulation (SNS), which is the main topic of this mini-review.

Vagal nerve stimulation for GI motility

VNS can be implemented permanently or chronically via stimulation electrodes placed at the vagus nerve and a pulse generator implanted in a subcutaneous pouch in the chest or abdomen. VNS using implantable devices has received FDA (Food and Drug Administration) approval for treating epilepsy, major depression disorders, heart failure and obesity (6). However, none of the surgically implanted devices has received regulatory approval for treating any of GI diseases (7).

Alternatively, VNS can be implemented noninvasively via transcutaneous stimulation of the vagus nerve, such as transcutaneous auricular vagal nerve stimulation (taVNS) and

transcutaneous cervical vagal nerve stimulation (tcVNS) (8). Both of these methods have been under investigation for treating GI diseases.

1. Transcutaneous auricular VNS

taVNS is accomplished by placing a pair of stimulation electrodes in the ear, usually in the symba concha as this area is 100% innervated with vagal afferent nerve. Both unilateral (both stimulation electrodes in one ear) and bilateral (one stimulation electrode in each ear) taVNS have been reported; however, there is no published studies comparing difference between unilateral and bilateral stimulation.

1.1 taVNS for functional dyspepsia (FD): In a recent study, taVNS was performed in 36 patients with FD. A clipper-like carbon electrode was placed in the symba concha of each ear (9). Electrical stimulation was performed by a watch-size portable device using a special parameter set (2s-on, 3s-off, 25Hz, 0.5ms and maximal tolerable current output) that was known to improve GI motility in other methods of neuromodulation (10). taVNS was delivered at home one hour, twice daily for 2 weeks. A significant improvement in symptoms of FD and anxiety/depression was observed with the taVNS, which was not noted with the sham stimulation (same electrical stimulation delivered at the elbow). Physiologically, a significant improvement was reported in gastric accommodation (assessed by a nutrient drink test) and gastric pace-making activity (assessed by noninvasive electrogastrogram). Impaired gastric accommodation and gastric pace-making activity have been frequently reported in patients with FD. The improvement in these measurements suggested restoration of these gastric physiological functions with the taVNS treatment. Mechanistically, the 2-week taVNS increased vagal efferent activity assessed by the spectral analysis of analysis of heart rate variability derived from the electrocardiogram. It was postulated that taVNS ameliorated FD symptoms by restoring gastric motility functions mediated via the vago-vagal pathway.

1.2 taVNS for irritable bowel syndrome (IBS) in adults: In another study, similar taVNS was performed in 42 patients with constipation-dominant IBS (IBS-C) (11). The patients were randomized to receive taVNS via silicon electrodes placed at bilateral symba concha or sham electrical stimulation (via the elbow). The stimulation was performed at home, 30min twice daily for 4 weeks. It was reported that in comparison with sham stimulation, taVNS significant and substantially increased the weekly number of complete spontaneous bowel movements, decreased abdominal pain and improve overall symptoms of IBS and quality of life. Symptoms of anxiety and depression were also improved with taVNS, compared with both baseline and sham stimulation. Physiologically, taVNS improved recto-anal inhibitory reflex (a rectal distention-induced relaxation of internal anal sphincter) and improved rectal sensation to rectal distention. Mechanically, taVNS enhanced vagal efferent activity assessed by the spectral analysis of heart rate variability and reduced proinflammatory cytokines (TNF-α and IL-6) and serotonin. Furthermore, the weekly number of complete spontaneous bowel movements was significantly correlated with the vagal efferent activity, suggesting a parasympathetic pathway involved in the enhanced colon motility.

Most interesting and intriguing findings of this study were the improvement in rectal sensation and rectal distention-induced relaxation of the internal anal sphincter, suggesting **a**

vagal afferent and sacral efferent pathway. This is because the rectum and anal sphincter are not innervated with the vagus nerve but the sacral nerve. We postulate that these effects were mediated via the vagal-sacral pathway as follows: taVNS activated NTS that projected to other parts of the brain to yield an enhanced sacral efferent activity, acting on the rectum and anal sphincter. In a rodent model of opioid-induced constipation, aVNS with similar stimulation parameters was reported to accelerate transit of the distal colon (not innervated with the vagus nerve) with a concurrent increase in activated neurons in the NTS (12). These findings suggest that aVNS may alter colorectum motility and sensation via both vago-vagal pathway and vago-sacral pathway (see Figure 1).

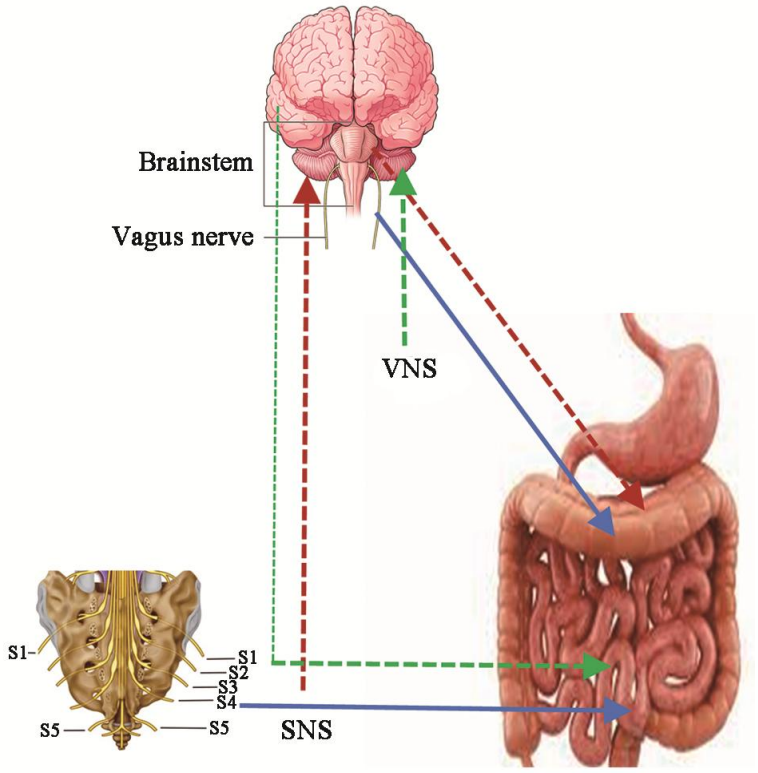

Figure 1: Parasympathetic pathways involved in vagal/sacral nerve stimulation. Solid blue: vagal/sacral efferent pathway; broken green: vagal afferent-sacral efferent pathway of VNS; broken red: sacral afferent-vagal efferent pathway of SNS.

1.3 Percutaneous aVNS for IBS in adolescents: Rather than with the use of surface electrodes, 2-mm needles were used for stimulation in an aVNS study in adolescents with IBS (13). The authors called it percutaneous electrical nerve field stimulation (PENFS). The stimulation was performed via 2-mm needles placed at different areas of one ear via a small pulse generator attached to the back of the ear. Instead of delivering constant current, the device delivered 3.2 V 1ms pulses alternating at 1 and 10 Hz frequencies every 2 second, with 2 hours-on and 2 hours-off. The treatment was administered 5 days/week for 4 weeks. The study outcome was the % of responders with the PENFS (N=27) compared with sham-treatment (a mock device with no stimulation output (N=23). The responder was defined as a decrease of 30% or more in the worst

abdominal pain score from baseline to 3 weeks of the therapy. It was found that the % of responders were significantly higher with the PENFS than the sham treatment (59% vs. 26%, P=0.024). No physiological or mechanistic outcomes were assessed.

The same therapy was applied for treating abdominal pain in adolescent patients with functional GI diseases (IBS, FD, abdominal migraine, functional abdominal pain or functional abdominal pain syndrome) (14). A significant reduction in worst abdominal pain score was reported after a 3-week treatment (N=60), compared with the sham treatment (no stimulation).

2. Transcutaneous cervical VNS for gastroparesis

tcVNS is performed by placing electrical stimulation transcutaneously over the cervical vagus nerve. tcVNS using a hand-held device (gammaCore) has been approved for treating cluster headache and migraine and is being explore for treating complications of COVID-19 infections (15). A recent open-label clinical trial explored its application for treating gastroparesis. In this study, tcVNS was performed a few minutes daily via a hand-held device for a period of 4 week in 15 patients with idiopathic gastroparesis (16). A moderate but significant decrease (about 35%) was noted at the end of the treatment in the total gastroparesis symptom score. Concurrently, tcVNS also improved gastric emptying assessed by the breath test. While this single-center uncontrolled study with a very small number of patients suggested a therapeutic potential of tcVNS for gastroparesis, more follow-up research is needed to demonstrate its clinical efficacy and possible mechanisms.

Sacral nerve stimulation for GI motility

Due to its anatomical innervation, electrical stimulation of the sacral nerve is developed for treating diseases of pelvic organs. SNS has been approved by FDA for treating overactive bladder and urinary incontinence as well as fecal incontinence (17). It has also been explored for treating constipation, ulcerative colitis and irritable bowel syndrome. Interestingly, recent preclinical studies have revealed its potential for treating disorders of GI organs not innervated by the sacral nerve, suggesting a sacral afferent and vagal efferent pathway. Methodologically, SNS has to be performed using surgically implanted electrodes and transcutaneous stimulation over the sacral nerve is less feasible due to the depth of the nerve underneath the skin.

1. Sacral nerve stimulation for fecal incontinence (FC)

SNS has been approved in most of countries in the world for treating FC that affects about 7% to 15% of general population (18). In this method, electrical stimulation is delivered via chronically implanted electrodes at S3 and an implantable pulse generator placed at a subcutaneous pouch in the buttocks. The stimulation is performed continuously with a frequency of 14Hz, pulse width of 210μs and voltage of 1-10 v based on patient's perception (19).

Clinically, SNS is used for treating chronic FD in patients who have failed or are not candidates for medical or physical therapy. The success rate was reported in large clinical trials to be around 80%, defined as a reduction in more than 50% of FC episodes (20). The SNS mechanisms for FC are largely unknown but some studies have demonstrated an increase in anal sphincter pressure and rectal sensation (19).

2. Sacral nerve stimulation for chronic constipation

Chronic constipation affects about 16% of adults worldwide (21) and classified as slow transit constipation, defecatory disorder and normal transit constipation. SNS has been investigated for treating chronic constipation for more than 30 years; however, it has not yet received regulatory approval for treating constipation (22). Although numerous clinical studies have been performed, recent systematic review and meta-analysis revealed ineffectiveness of SNS for constipation (23).

The major issue on the proposed SNS therapy for constipation is the selection of stimulation parameters. Although constipation is a totally different or physiologically opposite disease of FC, the proposed SNS therapy for constipation adopted the same stimulation parameters. More studies are needed to optimize stimulation parameters and SNS modalities for treating constipation.

3. Sacral nerve stimulation for irritable bowel syndrome

A few clinical studies have explored therapeutic potential of SNS for IBS that is one of most common forms of functional GI disorders. The major clinical symptom is abdominal pain in conjunction with constipation or diarrhea or both. The method used in the clinical studies adopted the same SNS method as used for treating FC (24). In a recent randomized clinical trial, SNS was performed using an implanted device in 21 patients with IBS and improved abdominal pain and IBS symptoms during a 2-week SNS period, compared with a 2-week device-off period (25).

Similar to SNS for constipation, more basic and translational research is needed to optimize stimulation parameters and treatment modalities. Since abdominal pain is the hallmark of IBS, SNS should be designed and optimized for treating visceral hypersensitivity that is one of major pathophysiologies of pain in IBS. In a recent animal study, SNS with a different set of stimulation parameters and treatment duration was reported to significantly ameliorate abdominal pain (26).

4. Sacral nerve stimulation for upper GI disorders

As discussed earlier, the upper GI tract, such as the stomach and small intestine, is innervated with the vagus nerve but not the sacral nerve. Accordingly, there has been absence of clinical studies exploring SNS for upper GI disorders. However, in a few recent animal studies performed in our lab, SNS was found to improve upper GI dysmotility mediated via the sacral afferent and vagal efferent pathway.

In one rodent study, acute SNS with parameters known to enhance parasympathetic activity (5Hz, 0.5ms, 10s on and 90s off) was reported to induce gastric fundic relaxation and increase gastric accommodation mediated via the sacral-vagal reflex (27). Concurrent mechanistic findings demonstrated SNS-induced activation of neurons in the nucleus tractus solitarius, enhancement of vagal efferent activity and release of nitric oxide in the gastric fundus.

In another rodent study (28), acute SNS with the same parameters reported in (27) improved gastric and duodenal slow waves impaired by rectal distention and normalized gastric emptying and small intestinal transit delayed by glucagon injection and rectal distention. Mechanistically, SNS enhanced vagal efferent activity, suggesting the same sacral-vagal pathway.

Perspectives of parasympathetic neuromodulation for GI diseases

While parasympathetic activity regulates GI motility endogenously, electrical stimulation of the parasympathetic nerves can also be used to regulate GI motility and treat functional GI diseases exogenously. Most commonly, electrical stimulation location is determined by the neuroanatomy of the parasympathetic nerves, i.e., stimulating the nerves that are directly linked to (innervated with) a target organ. However, recent animal and clinical studies seem to suggest that it is possible to apply neuromodulation of one branch of the parasympathetic nerves to alter functions of an organ that is only innervated by another branch of the parasympathetic nerves via the cross-branch pathway (sacral-vagal or vagal-sacral).

Neuromodulation of the parasympathetic nerves using implantable device has great potentials in treating chronic and severe functional GI diseases. However, more efforts are needed to optimize stimulation parameters and treatment regimens, such as SNS for constipation and IBS. More basic and translational research is needed to understand mechanisms of action involved in various applications of SNS and VNS. While the sacral nerve has been considered traditionally as a parasympathetic nerve, there was a study suggesting that the sacral autonomic outflow was sympathetic (29). However, the statement was not substantiated (30-31).

Noninvasive neuromodulation, such as taVNS and tcVNS, is attractive in functional GI diseases as these are common yet not life-threatening diseases. Scientifically, more mechanistic research is needed to optimize the therapy and thus improve its efficacy. Clinically, multi-center randomized clinical trials are necessary to demonstrate its therapeutic potentials in treating various diseases. Technologically, novel wearable devices should be developed that are easy to use daily and less visible (looks like an entertaining rather than a medical apparatus).

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References

1. Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. Adv Exp Med Biol. 2014;817:39-71. doi: 10.1007/978-1-4939-0897-4_3.
2. Beyak MJ, Bulmer DCE, Jiang W, Keating C, Rong W, Grundy D. Extrinsic sensory afferent nerves innervating the gastrointestinal tract. In: Johnson LR, ed. Physiology of the Gastrointestinal Tract, Vol 1, 5th edn. Amsterdam: Academic Press, 2006: 685–725.
3. Chen BN, Olsson C, Sharrad DF, Brookes SJ. Sensory innervation of the guinea pig colon and rectum compared using retrograde tracing and immunohistochemistry. Neurogastroenterol Motil. 2016 Sep;28(9):1306-16. doi: 10.1111/nmo.12825.
4. Gary H. Anatomy, descriptive and surgical: Gray's anatomy. Philadelphia: Courage Books/Running Press, 1974
5. Countee RW. Extrinsic neural influences on gastrointestinal motility. Am Surg. 1977 Sep;43(9):621-6. PMID: 20014.

6. Ogbonnaya S, Kaliaperumal C. Vagal nerve stimulator: Evolving trends. J Nat Sci Biol Med. 2013 Jan;4(1):8-13. doi: 10.4103/0976-9668.107254.
7. Bonaz B, Sinniger V, Pellissier S. Vagus Nerve Stimulation at the Interface of Brain-Gut Interactions. Cold Spring Harb Perspect Med. 2019 Aug 1;9(8):a034199. doi: 10.1101/cshperspect.a034199.
8. Thompson SL, O'Leary GH, Austelle CW, Gruber E, Kahn AT, Manett AJ, Short B, Badran BW. A Review of Parameter Settings for Invasive and Non-invasive Vagus Nerve Stimulation (VNS) Applied in Neurological and Psychiatric Disorders. Front Neurosci. 2021 Jul 13;15:709436. doi: 10.3389/fnins.2021.709436.
9. Zhu Y, Xu F, Lu D, Rong P, Cheng J, Li M, Gong Y, Sun C, Wei W, Lin L, Chen JDZ. Transcutaneous auricular vagal nerve stimulation improves functional dyspepsia by enhancing vagal efferent activity. Am J Physiol Gastrointest Liver Physiol. 2021 May 1;320(5):G700-G711. doi: 10.1152/ajpgi.00426.2020.
10. Chen JD, Yin J, Wei W. Electrical therapies for gastrointestinal motility disorders. Expert Rev Gastroenterol Hepatol. 2017 May;11(5):407-418. doi: 10.1080/17474124.2017.1298441.
11. Shi X, Hu Y, Zhang B, Li W, Chen JD, Liu F. Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. JCI Insight. 2021 Jul 22;6(14):e150052. doi: 10.1172/jci.insight.150052.
12. Zhang Y, Lu T, Meng Y, Maisiyiti A, Dong Y, Li S, Chen Y, Yin J, Chen JDZ. Auricular Vagal Nerve Stimulation Improves Constipation by Enhancing Colon Motility via the Central-Vagal Efferent Pathway in Opioid-Induced Constipated Rats. Neuromodulation. 2021 Oct;24(7):1258-1268. doi: 10.1111/ner.13406.
13. Krasaelap A, Sood MR, Li BUK, Unteutsch R, Yan K, Nugent M, Simpson P, Kovacic K. Efficacy of Auricular Neurostimulation in Adolescents With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial. Clin Gastroenterol Hepatol. 2020 Aug;18(9):1987-1994.e2. doi: 10.1016/j.cgh.2019.10.012.
14. Kovacic K, Hainsworth K, Sood M, Chelimsky G, Unteutsch R, Nugent M, Simpson P, Miranda A. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. Lancet Gastroenterol Hepatol. 2017 Oct;2(10):727-737. doi: 10.1016/S2468-1253(17)30253-4.
15. Czura CJ, Bikson M, Charvet L, Chen JDZ, Franke M, Fudim M, Grigsby E, Hamner S, Huston JM, Khodaparast N, Krames E, Simon BJ, Staats P and Vonck K (2022) Neuromodulation Strategies to Reduce Inflammation and Improve Lung Complications in COVID-19 Patients. Front. Neurol. 13:897124. doi: 10.3389/fneur.2022.897124
16. Gottfried-Blackmore A, Adler EP, Fernandez-Becker N, Clarke J, Habtezion A, Nguyen L. Open-label pilot study: Non-invasive vagal nerve stimulation improves symptoms and gastric emptying in patients with idiopathic gastroparesis. Neurogastroenterol Motil. 2020 Apr;32(4):e13769. doi: 10.1111/nmo.13769.
17. Yang G, Xu Y, Qu G, Zhang Y. Refractory overactive bladder patients who chose sacral neuromodulation therapy after failed OnabotulinumtoxinA treatment: A systematic review and meta-analysis. PLoS One. 2020 Mar 30;15(3):e0230355. doi: 10.1371/journal.pone.0230355.

18. Bharucha, A. E., Dunivan, G., Goode, P. S., Lukacz, E. S., Markland, A. D., Matthews, C. A., Mott, L., Rogers, R. G., Zinsmeister, A. R., Whitehead, W. E., Rao, S. S., & Hamilton, F. A. (2015). Epidemiology, pathophysiology, and classification of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop. The American journal of gastroenterology, 110(1), 127–136. https://doi.org/10.1038/ajg.2014.396
19. Matzel, K. E., Stadelmaier, U., Hohenfellner, M., & Hohenberger, W. (2001). Chronic sacral spinal nerve stimulation for fecal incontinence: long-term results with foramen and cuff electrodes. Diseases of the colon and rectum, 44(1), 59–66. doi: 10.1007/BF02234822
20. Thin, N. N., Horrocks, E. J., Hotouras, A., Palit, S., Thaha, M. A., Chan, C. L., Matzel, K. E., & Knowles, C. H. (2013). Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. The British journal of surgery, 100(11), 1430–1447. https://doi.org/10.1002/bjs.9226
21. Bharucha, A. E., Pemberton, J. H., & Locke, G. R., 3rd (2013). American Gastroenterological Association technical review on constipation. Gastroenterology, 144(1), 218–238. https://doi.org/10.1053/j.gastro.2012.10.028
22. MacDonagh, R. P., Sun, W. M., Smallwood, R., Forster, D., & Read, N. W. (1990). Control of defecation in patients with spinal injuries by stimulation of sacral anterior nerve roots. BMJ (Clinical research ed.), 300(6738), 1494–1497. https://doi.org/10.1136/bmj.300.6738.1494
23. Thaha, M. A., Abukar, A. A., Thin, N. N., Ramsanahie, A., & Knowles, C. H. (2015). Sacral nerve stimulation for faecal incontinence and constipation in adults. The Cochrane database of systematic reviews, (8), CD004464. https://doi.org/10.1002/14651858.CD004464.pub3
24. Fassov, J. L., Lundby, L., Laurberg, S., Buntzen, S., & Krogh, K. (2014). A randomized, controlled, crossover study of sacral nerve stimulation for irritable bowel syndrome. Annals of surgery, 260(1), 31–36. https://doi.org/10.1097/SLA.0000000000000559
25. Fassov, J., Lundby, L., Laurberg, S., & Krogh, K. (2019). Sacral nerve modulation for irritable bowel syndrome: A randomized, double-blinded, placebo-controlled crossover study. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society, 31(6), e13570. https://doi.org/10.1111/nmo.13570
26. Jiang L, Zhang N, Zhang S, Chen JD. Sacral nerve stimulation with optimized parameters improves visceral hypersensitivity in rats mediated via the autonomic pathway. Mol Pain. 2019 Jan-Dec;15:1744806919880651. doi: 10.1177/1744806919880651.
27. Ye F, Liu Y, Li S, Zhang S, Foreman RD, Chen JD. Sacral nerve stimulation increases gastric accommodation in rats: a spinal afferent and vagal efferent pathway. Am J Physiol Gastrointest Liver Physiol. 2020 Mar 1;318(3):G574-G581. doi: 10.1152/ajpgi.00255.2019.
28. Wang X, Zhang S, Pasricha PJ, Chen JDZ. Ameliorating effects of sacral neuromodulation on gastric and small intestinal dysmotility mediated via a sacral afferent-vagal efferent pathway. Neurogastroenterol Motil. 2020 Jul;32(7):e13837. doi: 10.1111/nmo.13837. Epub 2020 Mar 19. PMID: 32189439.
29. Espinosa-Medina I, Saha O, Boismoreau F, Chettouh Z, Rossi F, Richardson WD, Brunet JF. The sacral autonomic outflow is sympathetic. Science. 2016 Nov 18;354(6314):893-897. doi: 10.1126/science.aah5454.

30. Neuhuber W, Mclachlan E, Jänig W. The Sacral Autonomic Outflow Is Spinal, but Not "Sympathetic". Anat Rec (Hoboken). 2017 Aug;300(8):1369-1370. doi: 10.1002/ar.23600.
31. Horn JP. The sacral autonomic outflow is parasympathetic: Langley got it right. Clin Auton Res. 2018 Apr;28(2):181-185. doi: 10.1007/s10286-018-0510-6.