GASTROINTESTINAL DYSMOTILITY ASSOCIATED WITH SPINAL PATHOLOGY

GASTROINTESTINAL DYSMOTILITY ASSOCIATED WITH SPINAL PATHOLOGY: DIAGNOSIS AND TREATMENT USING NON-INVASIVE NEUROMODULATION

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Lay Abstract

There are gaps in the diagnosis process of complex gastrointestinal (GI) dysmotility disorders, including lack of testing of autonomic function, leaving patients suffering with diminished quality of life with unsuccessful treatment attempts. As many patients also experience injury or conditions of the spine, I have hypothesized that GI symptoms may be related to spinal injury-induced dysfunction of the autonomic nervous system. Experimental models aim to understand the location and nature of spinal pathology with GI symptoms for future diagnoses, as well as potential treatment options such as neuromodulation. Findings of this thesis suggest symptoms indicative of particular thoracolumbar spinal pathology and promising results of transcutaneous electrical nerve stimulation (TENS) to alleviate GI symptoms, including T3-T9 and T10-L2 spinal pathology-related postprandial abdominal pain, constipation, nausea, and vomiting. This work offers information for the diagnostic process of GI dysmotility and the future design of clinical trials of neuromodulation therapies.

Abstract

Chronic refractory gastrointestinal (GI) motility disorders are a significant burden on the healthcare system, acting as a large public health issue with significant impact on the quality of life in both the pediatric and adult population. Control systems of gastrointestinal motility are complex and involve coordination of smooth muscle contraction and relaxation, which the autonomic nervous system is largely responsible for. Gaps in the diagnosis process, such as overlooking autonomic function, has left patients with diminished quality of life and limited treatment options.

Many patients in the clinic have experienced injury within the spinal cord and we hypothesized that GI symptoms might be related to spinal injury causing disruption of sensory and/or motor nerves of the autonomic nervous system. Our objective became to better understand the specific location and nature of spinal injuries and GI symptoms, as completed through the development of a self-report questionnaire. Main findings suggest symptoms indicative of T3-T9 and T10-L2 spinal pathology.

COVID-19 did not allow for in-clinic neuromodulation with autonomic assessments, resulting in experiments remotely assessing at-home neuromodulation treatment for GI symptoms with suspected spinal autonomic dysfunction. At-home neuromodulation was not suitable for many patients, but those who were able to manage it showed highly promising results. After years of suffering, transcutaneous electrical nerve stimulation alleviated symptoms, particularly postprandial abdominal pain, constipation, vomiting and nausea. I discuss what we learned to set us up for successful at-home treatment, and we will use all information to design randomized controlled trials to prove the benefit of TENS.

The present work offers significant information on the relationship of thoracolumbar spinal pathology and complex GI symptoms, which is now used in the clinic in the diagnosis process of GI dysmotility. In addition, we have learned how to conduct at-home treatment using TENS, which allows us to execute future studies.

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Abbreviations

TENS: Transcutaneous electrical nerve stimulation
LLLT: Low-level laser therapy
DRG: Dorsal root ganglia
SMA: Superior mesenteric artery
ASD: Autism spectrum disorder
HRV: Heart rate variability
RSA: Respiratory sinus arrythmia
ANS: Autonomic nervous system
ENS: Enteric nervous system
SPW: Simultaneous pressure wave
HAPW: High amplitude pressure wave
RMSSD: Root mean square of successive differences between heartbeats
BPM: beats per minute
LES: Lower esophageal sphincter
TLESR: Transient lower esophageal sphincter relaxation
HRCM: High resolution colonic manometry
FGID: Functional gastrointestinal disorder

1 General Introduction

1.1 Research focus

The Chen-Huizinga Lab focuses on human physiology of gastrointestinal (GI) motility and the pathophysiology of GI dysmotility, aiming to understand the control mechanisms and to explore clinical symptom markers for the diagnosis and for guiding optimal management. Our previous clinical research on chronic constipation and fecal incontinence has investigated several manometric colonic motor patterns which could be used as indicators of colonic dysmotility. Our lab developed the use of High-Resolution Colonic Manometry (HRCM) and Heart Rate Variability (HRV) as diagnostic tools for colonic dysmotility and autonomic dysfunction, as well as several non-invasive neuromodulation techniques as potential treatments of autonomic dysfunction-related GI dysmotility, such as Low-Level Laser Therapy (LLLT) and Transcutaneous Electrical Nerve Stimulation (TENS).

My project focuses on spinal pathology-related severe GI dysmotility, which is a challenging clinical scenario, associated with severe abdominal pain and difficulty of oral food intake, that may require visits to the emergency department, hospitalization, and nutritional support. So far, there is no effective pharmacological treatment. Underlying mechanisms are still largely unknown.

Our aim was to develop methods to diagnose autonomic dysfunction and develop treatments to restore autonomic reflexes. To thoroughly familiarize myself with measurements of autonomic functioning I reviewed the literature on autonomic dysfunction in children with autism since this is a special interest of mine. We discovered that much of this literature treats autonomic measurements too superficially and often comes to wrong conclusions. We decided to write a review article on this which became chapter 5 of my thesis. Measuring autonomic dysfunction in our patients did not materialize because of COVID 19 restrictions.

Many refractory patients with functional gastrointestinal disorders (FGIDs) have shown positive spinal findings, including acute or chronic spinal injury. Based on neuroanatomy, we hypothesized that these GI symptoms might be related to disruption of sensory and/or motor innervation of the autonomic nervous system. Our objective became to better understand the specific location and nature of spinal injuries and these GI symptoms. This was completed through the development of a self-report questionnaire to allow for the collection of symptom-related data and spinal diagnostic imaging studies, which is reported in chapter 2.

Our initial goal was to combine in-person neuromodulation with autonomic assessments, but limitations due to the COVID-19 pandemic had enormous influence on in-person clinical research. Consequently, we started to experiment with techniques to remotely assess autonomic functioning and at home treatment of GI symptoms suspected of being due to spinal autonomic dysfunction using TENS. The latter study became chapters 3 and 4.

1.2 Gastrointestinal dysmotility

Gastrointestinal motility disorders are described as disorders of the processes and coordination of smooth muscle contraction and relaxation of the gastrointestinal tract to propagate material through the tract and end with defecation (Deane, Chapman, Reintam Blaser, McClave, & Emmanuel, 2019). GI dysmotility includes esophageal dysmotility, gastric dysmotility,small intestinal dysmotility, colonic dysmotility, and anorectal dysmotility. Esophageal dysmotility includes conditions such as gastroesophageal reflux disease (GERD), achalasia and ineffective esophageal motility, and can be diagnosed based on specific contractile patterns seen on esophageal manometry (Wilkinson & Halland, 2020). Treatment of esophageal dysmotility include lifestyle modificaton, some pharmacotherapies and surgical therapies (Wilkinson & Halland, 2020). Gastric dysmotility such as gastroparesis involves delayed gastric emptying of solid food and can be diagnosed via a gastric emptying study, such as gastric scintigraphy or breath test (Camilleri et al., 2018). Treatment of such conditions rely on dietary modification or prokinetic drugs to stimulate gastric motor activity (Camilleri et al., 2018). Patients with gastric dysmotility may also have gastroparesis-like symptoms without delayed gastric emptying, such as chronic unexplained nausea and vomiting (CUNV) (Pasricha et al., 2011). Small intestinal dysmotility such as small bowel pseudo-obstruction can be diagnosed via abdominal CT with oral and intravenous gastrografin contrast and is primarily treated with surgical intervention (Rami Reddy & Cappell, 2017). Chronic constipation is a disorder of colonic motility and is the most common defecation disorder in North America, with a prevalence up to 35% of adult populations and up to 30% in child populations (Mugie, Benninga, & Di Lorenzo, 2011). Treatments of chronic constipation include lifestyle and diet modifcations or laxative therapy (Jani & Marsicano, 2018). Anorectal dysmotility disorders include fecal incontinence, which is typically treated with lifestyle and diet modifcation, anorectal biofeedback training, medication therapies or surgical intervention (Mellgren, 2010).

Most of the dysmotility diagnoses are pathophysiological diagnoses, such as ineffective esophageal motility and slow colonic transit. There are often overlapping conditions, such as GERD and hypotensive lower esophageal sphincter, distal colon dysmotility and anorectal dysfunction. Since the gut works coordinately, patients may be diagnosed with a range of complex dysmotility of the upper GI tract, including the

esophagus, stomach, small intestine, proximal colon, or the distal colon including the descending colon, sigmoid colon, rectum and anal sphincters.

Autonomic innervation plays a key role in gastrointestinal motility and the defecation process, providing extrinsic neural input to regulate, modulate, and control motility functions (Browning & Travagli, 2014). In general, the parasympathetic branch of the autonomic nervous system is responsible for excitatory control of GI motility, while the sympathetic branch is responsible for inhibitory control of GI motility (Browning & Travagli, 2014). In the last few years, our lab has developed several parameters for the assessment of parasympathetic tone and reactivity and sympathetic tone and reactivity in patients with severe GI dysmotility such as chronic constipation. Currently, autonomic activity can be measured using HRV parameters such as respiratory sinus arrythmia (RSA), root mean squared successive differences (RMSSD), and the sympathetic parameter, the Baesky's stress index (SI) (Xhyheri, Manfrini, Mazzolini, Pizzi, & Bugiardini, 2012). We see the understanding of autonomic activity and its relation to GI motility as critically important in order to gain a better understanding of the pathophysiology in patients with severe GI motility disorders; we see this as a prerequisite for optimal management.

1.3 Non-invasive neuromodulation

Galvani first demonstrated that neurons could be electrically stimulated in the 18th century and developed the theory of electrical excitation (Galvani, 1794) (Galvani, 1841) (Verkhratsky, Krishtal, & Petersen, 2006), eventually leading to the development of neuromodulation. Neuromodulation is stimulation, inhibition, or regulation of central, peripheral, or autonomic nervous system activity (Krames, Peckham, Rezai, & Aboelsaad, 2009). The gate control theory of pain proposed by Melzack & Wall (Melzack & Wall, 1965) lead to the first use of electrical neuromodulation of the dorsal column of the spinal cord to treat chronic pain (Shealy, Taslitz, Mortimer, & Becker, 1967) (Shealy, Mortimer, & Reswick, 1967). Neuromodulation has since emerged to aid in various clinical applications, such as prosthetics, regulation of various body functions, and neuroscience research (Luan, Williams, Nikolic, & Constandinou, 2014). Invasive forms of neuromodulation, such as implantable devices, have become popular for conditions such as urinary incontinence (Grünewald, 1998). However, the invasiveness of such neuromodulation treatments brings disadvantages such as high cost, risk of surgical complication, potential risk for hardware-related complications and adverse effects such as further neurological damage (Chen et al., 2020).

Non-invasive neuromodulation involves direct stimulation of nerves, most often electrical stimulation, to generate action potentials within the neural networks that regulate the body's organs to affect the central and peripheral nervous systems (Luan, Williams, Nikolic, & Constandinou, 2014). The non-invasive nature of this treatment is low-risk and low-cost, allowing for low-risk stimulation of delicate extrinsic innervation

pathways involved in GI motility. Non-invasive neuromodulation treatments such as transcutaneous electrical nerve stimulation (TENS) have been used successfully to treat patients with chronic constipation due to the inability to evoke a normal defecation reflex (Veiga, Lordêlo, Farias, & Barroso, 2013).

Low-level laser therapy (LLLT) is a non-invasive form of neuromodulation, involving the use of red LED light, infrared LED light and infrared laser light to modulate spinal nerves. Our lab evaluated the effects of LLLT on autonomic function after one session of sacral photobiomodulation in patients with chronic constipation. During the treatment, autonomic functioning is evaluated by measuring changes in HRV parameters, reflecting both sympathetic and parasympathetic activity. Respiratory sinus arrythmia (RSA), root mean square for successive differences (RMSSD) and SD1 (a Poincaré plot component) are used to reflect parasympathetic activity, while the Baevsky's Stress Index (SI) is used to reflect sympathetic activity (Xhyheri, Manfrini, Mazzolini, Pizzi, & Bugiardini, 2012). After completing LLLT in 41 patients with colonic dysmotility, our lab found light arrays (red and infrared) to reduce parasympathetic activity and increase sympathetic activity; infrared laser probe increased parasympathetic activity and decreased sympathetic activity. The overall effect of one session of LLLT was, on average, a shift into the parasympathetic domain, primarily by inhibition of sympathetic activity. The recorded change in autonomic activity implies that LLLT successfully activated autonomic nerves. We have interpreted these results as a good indication of the potential for LLLT to stimulate autonomic nerves to treat chronic constipation. Through photobiomodulation, stimulation of autonomic nerves containing cell bodies in the dorsal root ganglia of the sacral spinal cord may trigger motor activity that evokes the defecation reflex.

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive form of nerve stimulation for therapeutic action (Moore, Gibson, & Burgell, 2018). It involves the passing of oscillating currents between surface electrodes to stimulate nerves within the area of focus (Payne, Furness, & Stebbing, 2019). Neuromodulation via TENS has shown to be an effective therapy for the treatment of colonic dysmotility, particularly constipation, via the stimulation of the autonomic nervous system in both children and adults (Veiga, Lordêlo, Farias, & Barroso, 2013).

1.4 Objectives

The objectives of my thesis work were:

1) to better understand the control mechanisms of human GI motility, particularly the role of the autonomic nervous system;
2) to develop and implement a self-report questionnaire as a diagnostic tool to assess severe GI dysmotility;

3) to implement TENS, applied by the patient at home, as a non-invasive neuromodulation treatment, and investigate its efficacy to treat severe GI dysmotility symptoms.

Several factors, including spinal conditions and anxiety, can together lead to a level of autonomic dysfunction that results in GI dysmotility and pain. It was our hypothesis that heart rate variability parameters would be useful as an assessment of autonomic function in patients with neurogenic impairment and to evaluate effectiveness of non-invasive, neuromodulation treatments for complex dysmotility patients, however, this goal has not been accomplished due to COVID-19 restrictions over the course of my MSc studies.

This thesis will report on the studies I have carried out, specifically:

1. Severe GI dysmotility cases involvement in Dr. Chen's clinic: N=39, including 2 case reports. I have worked on the theoretical aspects of the diagnosis and treatment of these patients, with a specific focus on associated spinal pathway pathology and other factors such as anxiety leading to autonomic dysfunction and resulting in GI symptoms. I have collected all patient's clinical information and have worked on classifying their clinical features based on neuroanatomy. I have analyzed their clinical symptoms using the self-report questionnaire to identify what clinical features are indicative of neurogenic impairment of GI motility. This is in part reflected by the case reports.

2. Home TENS treatment (thoracolumbar neuromodulation) for severe GI dysmotility. I have performed 41 cases of virtual home-TENS training independently. I have carried out regular follow up with cases. I have monitored their symptoms progression and evaluated the effectiveness of home-TENS treatment through questionnaires which I have developed to make the appropriate suggestions for future studies.

3. Autonomic dysfunction in patients with ASD. I have a special interest in patients with autism since I have been counselling such patients for several years. In order to further understand the role of ANS in human diseases in general and specific to autism, I have published a review article on the role of the autonomic nervous system in autism, including the role of the ANS in GI dysmotility in these patients (Barbier et al. 2022). It is our hypothesis that despite common conclusions in the autism literature, children with autism do not have autonomic dysfunction that can be related to their ASD diagnosis, however there are subgroups of autism patients such as those with anxiety or GI dysmotility disorders that affect autonomic reactivity.

1.5 Effect of the COVID-19 pandemic on my research

The COVID-19 pandemic has resulted in difficulties and limitations to conducting in-person clinical research as well as in-person treatment options for patients. This resulted in the shift of my focus to at-home TENS treatment, allowing patients to complete the low-risk, daily treatment at home. The virtual setting of the study brought issues with patient compliance, while the nature of the at-home treatment resulted in the lack of a placebo or sham group. The inaccessibility of in-person visits also made the completion of autonomic nervous system assessment not possible for patients. This made for the lack of data on patient autonomic function, which would have allowed for further confirmation of autonomic dysfunction-induced GI dysmotility, spinal pathology-induced autonomic dysfunction and autonomic response to TENS treatment.

1.6 Patient population

I have worked with Dr. Chen in her clinic on patients with complex chronic GI dysmotility. Patients were diagnosed with a range of complex dysmotility of the GI tract, including esophageal dysmotility, gastroparesis, small intestinal dysmotility, left colon dysmotility and anorectal dysmotility. Common symptoms among patients include pain in the upper abdomen and epigastric area, bloating, dysphagia, nausea, and vomiting. Patients also exhibited symptoms of colonic dysmotility, such as chronic constipation. The most common features of concern in this patient population are severe abdominal pain, bloating, nausea, vomiting, and dysphagia, however unremarkable GI investigations such as endoscopies, abdominal CTs, colonoscopies, etc. lead to the lack of a clear GI diagnosis outside of functional GI disorders. A large subgroup of patients has an associated spinal condition or spinal injury; these patients often exhibit symptoms of severe abdominal pain that radiates to the back. Patients with severe GI dysmotility and potential spinal pathology, without clear GI diagnosis other than functional GI disorders, were recruited into our study. We hypothesized the dominant pathophysiology of upper GI dysmotility patients to involve thoracic neurogenic impairment and therefore we focused on it for treatment.

These patients often had confirmed spinal injury or conditions within the thoracolumbar region of the spine. Our hypothesis was that the dominant pathophysiology was ongoing thoracic spinal nerve pathology, either due to spinal trauma/injury or worsening of previous diseases/conditions such as scoliosis, stenosis, or degenerative changes. Based on the neuroanatomy of extrinsic innervation of the gut, this spinal pathology may influence the autonomic and sensory pathways involved in GI motility and nociceptive perception, leading to GI symptoms such as severe abdominal pain with or without association of food intake. However, these neurological changes may be

reversible through management such as non-invasive neuromodulation. Therefore, we targeted the thoracic spinal nerves for the treatment of severe GI dysmotility symptoms through home-TENS.

1.7 Spinal innervation of the gut

1.7.1 The anatomy of human spinal cord and vertebrates

The human spinal cord can be divided into 21 segments, consisting of 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal segment (Bican, Minagar, & Pruitt, 2013). Each segment, with the exception of the first cervical segment, has a pair of dorsal (sensory) roots and a pair of ventral (motor) roots (Cho, 2015). Each dorsal and ventral root joins in the intervertebral foramina to form a spinal nerve, which exit the spinal canal through intervertebral foramina. Each dorsal root also forms a dorsal root ganglion outside of the spinal cord, containing the cell bodies of sensory neurons (afferent fibres) that are involved in visceral and somatic innervation. (Bican, Minagar, & Pruitt, 2013). The spinal cord is protected by the vertebral column, which intervertebral discs between each vertebrae provide cushioning and flexibility to the vertebral column (Cho, 2015).

1.7.2 The central nervous system and peripheral nervous system

The central nervous system (CNS) is comprised of the brain and the spinal cord, and it provides extrinsic neural inputs that modulate and control gastrointestinal functions such as digestion, nutrient absorption and motility (Browning & Travagli, 2014). The peripheral nervous system (PNS) is comprised of nerves that lay outside of the CNS and are composed of afferent sensory fibres and efferent motor fibres (Catala & Kubis, 2013). Sensory spinal nerves have cell bodies in the dorsal root ganglia (DRG) and together with motor spinal nerves make up the PNS (Catala & Kubis, 2013). The autonomic nervous system (ANS) is a component of the PNS and is comprised of the parasympathetic nervous system, sympathetic nervous system, and enteric nervous system (Wehrwein, Orer, & Barman, 2016). The ANS provides neural control of physiological processes of the body and contributes to the maintenance of homeostasis (Wehrwein, Orer, & Barman, 2016).

1.7.3 Somatic and visceral innervation

Visceral pain arises from soft tissue (muscles, ligaments and tendons) and/or internal organ damage (Van Oudenhove et al., 2020) and can occur from stimuli such as organ stretch or distension, organ hypoxia or ischemia, traction of the mesentery and chemical stimuli triggering inflammatory processes (Gebhart & Bielefeldt, 2016). Viscera have bilateral sensory innervation and are innervated by two sets of nerves: vagal and spinal

nerves (Gebhart & Bielefeldt, 2016). Visceral afferent fibres convey visceral sensation and pain to the CNS and are mainly composed of myelinated small-diameter A-δ fibres or unmyelinated C fibres. Similar to somatic afferents, visceral afferents have the cell bodies of their afferent neurons located in the DRG (Deer et al., 2019). Unlike somatic afferents however, many visceral afferent fibres traverse pre- and paravertebral ganglia (such as sympathetic chain ganglia) prior to reaching the spinal cord, where they may branch off to collateral nerves which play a role in the modulation of organ function (Gebhart & Bielefeldt, 2016). The fibres terminate in the laminae I & II of the spinal dorsal horn (Cervero, 1983) and projections influence autonomic (sympathetic and parasympathetic) efferent outflow in the intermediolateral cell column and sacral parasympathetic nucleus. Projections are also received by lamina X, surrounding the central canal (Ness & Gebhart, 1987) (Krotov et al., 2017). All second order spinal dorsal horn neurons that receive visceral input also receive convergent somatic input, this is referred to as the viscerosomatic convergence and is responsible for the referral of visceral sensation and pain to somatic sites(Gebhart & Bielefeldt, 2016), such as pelvic and/or colonic sensations being referred to the abdomen (Gebhart & Bielefeldt, 2016). During visceral pain, the thalamus, insula, and dorsal part of the anterior cingulate cortex are activated to assess sensory information (Dunckley et al., 2005).

Somatic pain and innervation also come from sensory spinal nerves, which cell bodies are contained in the DRG (Catala & Kubis, 2013) (Deer et al., 2019). Somatic afferent fibres are mainly composed of myelinated small-diameter A-δ fibres (Lumb, 2002) and convey extrinsic nerve-related pain to the CNS. In a study conducted by Cervero, electrical stimulation of the DRG resulted in the activation of somatic neurons, which are found in laminae II, III and IV of the dorsal horn (Cervero, 1983). Somatic sensory information is conveyed to the CNS and activates regions of the insular, cingulate and prefrontal cortices that are different from regions that assess visceral nociceptive information (Gebhart & Bielefeldt, 2016). Somatic pain involves the left dorsolateral pre-frontal cortex and bilateral inferior parietal cortex activation (Dunckley et al., 2005).

1.8 Neurodevelopment of the spinal cord

Embryonic development of the spinal cord and vertebral column begins with gastrulation. Gastrulation of an embryo results in the formation of three layers; the ectoderm, mesoderm and endoderm, and the formation of the notochord (Kaplan, Spivak, & Bendo, 2005). The mesoderm surrounding the notochord separates into three different areas: the paraxial, lateral, and intermediate areas. The paraxial area develops into somites, which can be differentiated into a dermomyotome or a sclerotome cell (Dias, 2007). Sclerotome cells eventually undergo fusion and develop into the skeleton of the vertebral column. The notochord is responsible for sending molecular signals to initiate proliferation of the ectoderm, which leads to the development of the nervous systems, as

well as signals initiating the development and ossification of the spinal vertebrae (Kaplan, Spivak, & Bendo, 2005). The embryonic development of the spinal cord begins with ectodermal proliferation, resulting in the formation of the neural plate, which ultimately involutes to form the neural tube (neurulation). Ectodermal proliferation also involves differentiation leading to the formation of neural crest cells at the border between the neural and surface ectoderm (Wilde, Petersen, & Niswander, 2014). Specification of cell types follows embryonic events such as neural tube closure and neural crest cell migration (Rogers & Nie, 2018). These neural crest cells undergo proliferation, migration, and differentiation, leading to the formation of various cell types, such as those involved in the formation of the central and peripheral nervous systems and in the formation of connective bones and tissue (Mayor & Theveneau, 2013). Neural crest cells are classified based on their level of origin, including cranial, which contribute to craniofacial bone/cartilage, nerve ganglia, smooth muscle, and connective tissue; cardiac, which contribute to heart development; vagal and sacral, which give rise to the enteric nervous system of the gastrointestinal tract; and trunk, which contributes to the formation of peripheral nervous system and endocrine system (Dash & Trainor, 2020). During neural tube closure, crest cells leave their origin site and migrate in a ventral to dorsal order (Krispin, Nitzan, Kassem, & Kalcheim, 2010) to localize and undergo differentiation (Ziller & Smith, 1982) based on environmental signals during migration (Mayor & Theveneau, 2013).

During the development process of neural crest cell differentiation, neural crest cells migrate and proliferate to form nerves surrounding gut structures, forming the enteric nervous system. The enteric nervous system (ENS) is involved in the neuronal control of digestive function and is comprised of an integrated reflex system providing intrinsic innervation to the GI tract, playing a large role in the regulation of gastrointestinal motility and secretion (Furness, Callaghan, Rivera, & Cho, 2014). The ENS derives from the neural crest, mostly originating from vagal segments of the neural crest (Lake & Heuckeroth, 2013) (Yntema & Hammond, 1954), and continues to proliferate and migrate in the intestinal wall forming enteric neural crest-derived cells (Lake & Heuckeroth, 2013). Neural crest cells deriving from the sacral segments of the neural crest are also found to contribute to the development of the distal bowel (colorectum) (Burns & Douarin, 1998). This migration begins prior to week 4 in human embryonic development and is complete by week 7 (Lake & Heuckeroth, 2013). Following migration, enteric neural crest-derived cells (ENCDCs) continue to proliferate and differentiate into glia and neuronal subtypes, forming a nervous system network throughout the intestinal tract (Lake & Heuckeroth, 2013). This process of development of the ENS is controlled by cell surface receptors and their ligands and transcription factors. This includes glial cell line-derived neurotrophic factor (GDNF) and its receptor RET, which supports the proliferation, migration, and differentiation of ENS precursor cells, endothelin-3 and its receptor endothelin receptor type B, which supports ENS development in the colon, and

transcription factors such as SOX10 and PHOX2B, which are important for colonization of ENCDCs in the bowel (Lake & Heuckeroth, 2013).

Both the dorsal root and sympathetic ganglia derive from trunk segments of the neural crest (Mayor & Theveneau, 2013) (Kasemeier-Kulesa, Kulesa, & Lefcort, 2005) and form during the embryonic development process of neural crest cell differentiation (Jacob, 2015). The dorsal root ganglia (DRG) are responsible for the transmission of somatosensory information from the periphery to the sensory perception centres in the CNS (Wiszniak & Schwarz, 2019). They are primarily comprised of two neural crest-derived cells: sensory neurons and glia (Wiszniak & Schwarz, 2019). Zirlinger et al. found that a subpopulation of neural crest cells expressing bHLH transcription factor *Ngn2* is more likely to develop into sensory neurons than autonomic (sympathetic) sub-lineages, which is commonly seen as the fate of alternative neural crest cells which express *Wnt1*. This however was not found in DRG, where neural crest cells expressing either *Ngn2* and *Wnt1* are equally likely to generate neurons or glia (Zirlinger, Lo, McMahon, McMahon, & Anderson, 2002). Within DRG, Notch signalling plays an important role in the differentiation of sensory neurons and glia during the development of the nervous system via lateral inhibition (Zirlinger, Lo, McMahon, McMahon, & Anderson, 2002) (Wakamatsu, Maynard, & Weston, 2000). Wakamatsu et al. found that neural crest cells which express *Delta1* (DLL1) develop into neuronal cells of the DRG and signal to adjacent cells via Notch receptors to inhibit neuronal differentiation in neighbouring cells, resulting in glial differentiation (Wakamatsu, Maynard, & Weston, 2000). Sympathetic chain ganglia arise from the same trunk neural crest cells as DRG (Dyson, Holmes, Li, & Kulesa, 2018). The trunk neural crest cells continue migrating ventrally past the DRG site and accumulate dorsolateral to the dorsal aorta to form the sympathetic ganglia (Kasemeier-Kulesa et al., 2005). Preganglionic fibres form and are contained in the lateral gray horn from T1-L2, which project to the sympathetic ganglion for sympathetic innervation (Purves et al., 2001). Sympathetic innervation from the thoracolumbar spine is responsible for the inhibition of gastrointestinal transit via inhibiting excitatory effects of enteric neurons in gastrointestinal muscle (Furness, Callaghan, Rivera, & Cho, 2014).

During embryologic development of vertebrae and the spinal cord, neural crest cells derived from the cranial and trunk levels of the neural crest migrate and result in the development adrenergic and cholinergic cells, making acetylcholine and catecholamines (Ziller & Smith, 1982). The synthesis of catecholamines has been suggested to occur after the interaction of neural crest cells and mesenchyme derivatives (Ziller & Smith, 1982). Catecholamines include neurotransmitters such as epinephrine and norepinephrine, which are released by the adrenal medulla and the nerve terminals of the sympathetic nervous system and are both highly important for the stress response. The stress response mediated by epinephrine and norepinephrine, commonly called the fight-

or-flight response, generate responses such as decreased visceral activity, increased heart rate and inhibition of processes such as digestion (Romero & Butler, 2007).

1.9 Common spinal pathology

The thoracic spine is the origin of 80% of axial rotation and has various muscular attachments of the scapulothoracic articulation, therefore playing a prominent role in movement of the upper extremities (Ruiz, Feigenbaum, & Best, 2020). The thoracolumbar junction region (T10-L2) is more prone to injury due to high involvement in axial rotation and upper extremity movements, as well as this region transitioning from the rigid thoracic region to the mobile lumbar region (Menzer, Gill, & Paterson, 2015). Sports and extracurricular activities involving repetitive loading of the spine, such as rowing, gymnastics, golf, and sports involving jumping (such as snowboarding and skiing) have shown to predominantly result in injuries to the thoracolumbar spine (Menzer, Gill, & Paterson, 2015). Rowing in particular has shown to have significant impact on the thoracolumbar spine due to large compressive forces on the spine while in a flexed position, resulting in frontal parts of intervertebral discs to be impacted with the primary load of the force (Willwacher, Koopmann, Dill, Kurz, & Brüggemann, 2021).

In adults aged 25-74, 8.3% of people were found to have scoliosis, with prevalence doubling among women (Carter & Haynes, 1987), likely due to higher risk of deformity progression during adolescence in females (Miller, 1999). Studies have found the prevalence of de novo scoliosis, or scoliosis associated with degenerative conditions of the spine, to be as high as 68% in adults ≥ 50 years old (Schwab et al., 2005). 50%-89% of scoliosis patients have resulting stenosis which may induce neurological symptoms and deficits, such as neurological pain or bowel/bladder dysfunction (Fu, Rhagavan, Shaffrey, Chernavvsky, & Smith, 2011) (Smith, Fu, Urban, & Shaffrey, 2008).

Spinal cord injury (SCI) has been found to have severe impact on autonomic function, including bladder and bowel control (Karlsson, 2006). Neurogenic bowel dysfunction, including constipation and fecal incontinence, is the most common secondary effect reported by SCI patients (Burns et al., 2015), in which lost defecation reflexes due to injury result in damage to sacral parasympathetic innervation of the GI tract (Callaghan, Furness, & Pustovit, 2018).

1.9.1 Superior mesenteric artery syndrome

Superior mesenteric artery (SMA) syndrome may account for the pathophysiology of some patients with upper GI dysmotility symptoms. The SMA forms an angle with the abdominal aorta and the third part of the duodenum sits within this angle (Warncke, Gursahaney, Mascolo, & Dee, 2019). SMA syndrome is a condition involving the

narrowing of the aortomesenteric angle, leading to proximal bowel obstruction of this part of the duodenum (Van Horne & Jackson, 2021) related to loss of intra-abdominal adipose tissue that sits beneath the SMA branching from the aorta (Warncke, Gursahaney, Mascolo, & Dee, 2019). This condition is most commonly seen following rapid weight loss which results in the reduced size of a retroperitoneal fat pad (Figure 1.1) or in patients following scoliosis-corrective surgery, in which the lengthening of the spine following surgery increases the tension of the mesentery therefore narrowing the aortomesenteric angle (Merrett, Wilson, Cosman, & Biankin, 2009). Compression of the third part of the duodenum leads to dilation of the gastric and proximal duodenum (Madhu, Govardhan, & Krishna, 2019). Patients experience intolerance of oral food intake and gastroparesis and symptoms such as nausea, vomiting and abdominal pain, particularly in the epigastric area (Merrett, Wilson, Cosman, & Biankin, 2009). The diagnosis of SMA if often missed and must be made with contrast X-ray studies, barium studies or CT imaging with oral contrast. Imaging will show dilation of the proximal duodenum and blocked passage of contrast beyond the third part of the duodenum (Merrett, Wilson, Cosman, & Biankin, 2009). Diagnosis of vascular abnormalities associated with SMA may be done with fine slice CT imaging with vascular reconstruction measuring the aortomesenteric angle, in which an angle less than 25° is consistent with diagnosis (Applegate & Cohen, 1988). Based on the neuroanatomy, thoracic spine pathology might be part of the pathophysiology of SMA syndrome. Further clinical research with a focus on the extrinsic autonomic innervation of the SMA and related duodenum may help to further understand the role of neurogenic impairment on SMA syndrome.

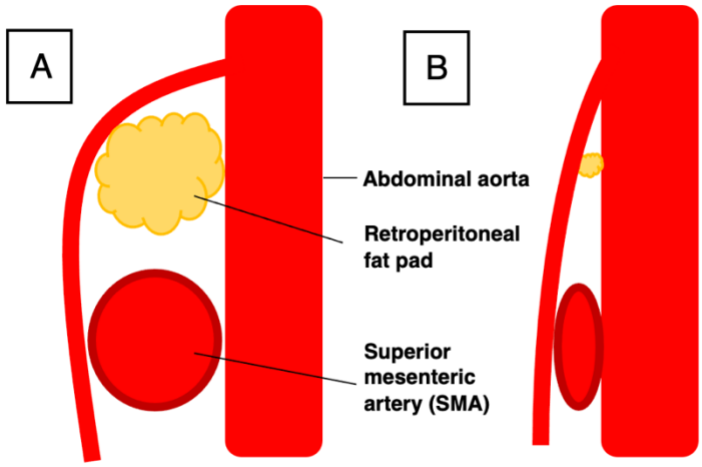

Figure 1.1 Schematic of superior mesenteric artery (SMA) syndrome
A. A normal aortomesenteric relationship with a retroperitoneal fat pad allowing the duodenum to pass through the two vessels unobstructed. **B.** Extrinsic compression of the duodenum between the superior mesenteric artery and the abdominal aorta due to reduced size of the retroperitoneal fat pad.

1.10 Involvement of the autonomic nervous system in patient pathophysiology

Extrinsic innervation of the autonomic nervous system (ANS) is essential to the defecation process (Devroede & Lamarche, 1974) . Devroede & Lamarche found that

loss or resection of pelvic splanchnic nerves, which are preganglionic parasympathetic nerve fibres, results in diminished ability to defecate and reduced colonic motility, particularly affecting the left colon. While sacral parasympathetic pathways innervate the distal gastrointestinal tract (Brookes, Dinning, & Gladman, 2009) , vagal parasympathetic efferents originating in the dorsal motor nucleus of the vagus (DMV) in the brainstem provide parasympathetic innervation of the upper gastrointestinal tract, including the stomach, small intestine and proximal colon (Browning & Travagli, 2014) .

Vagal Efferent Pathways

DMV neurons act as cholinergic preganglionic parasympathetic neurons, releasing acetylcholine for the activation of nicotinic receptors on postganglionic neurons of the target organ (Browning & Travagli, 2014). In upper GI motility, acetylcholine released from DMV neurons bind to nicotinic receptors on postganglionic neurons onto interstitial cells of Cajal (ICC) and myenteric neurons in the stomach and intestine (Browning & Travagli, 2014). The activation of muscarinic cholinergic receptors allows for smooth muscle contraction, playing a large role in the control of gastric tone and motility (Browning & Travagli, 2014).

Vagal Afferent Pathways

The upper GI tract is innervated by sensory neurons originating from the nodose ganglia and jugular ganglia, projecting via the vagus (Brookes, Spencer, Costa, & Zagorodnyuk, 2013) and synapsing in the nucleus tract solitarius with parasympathetic vagal efferents that originate from the DMV (Payne et al., 2019). Vagal mechanoreceptors with intraganglionic laminar endings (IGLEs) in myenteric ganglia use stretch-activated ion channels to detect distention of the upper GI tract (Brookes, Spencer, Costa, & Zagorodnyuk, 2013). This mechanism is useful in responding to sensations of gastric fullness. Vagal intramuscular afferent fibres form appositions with intramuscular ICC (Grundy et al., 2006), and have been suggested to work with ICC and smooth muscle to form complexes that function as stretch receptors within the gut wall (Powley & Phillips, 2011).

Thoracolumbar Afferent Pathways

The upper gastrointestinal tract is also innervated by thoracolumbar afferents (Payne et al., 2019), which project via the splanchnic nerves (Brookes, Spencer, Costa, & Zagorodnyuk, 2013). Thoracolumbar spinal afferents respond to nociceptive stimuli in the gut (Payne et al., 2019) and run parallel to sympathetic efferent pathways in the gut (Brookes et al., 2013). A study tested visceral sensation of the gut-evoked pain in the proximal regions of the gut (small intestine and proximal colon), finding that bilateral sympathectomy of the thoracolumbar spine resulted in the abolishment of pain in humans (Ray & Neill, 1947). These findings show that pain/nociceptive events in the upper GI

tract are mediated via thoracolumbar afferent pathways. Signals project from the DRG to brain centres and are there interpreted.

Thoracolumbar Efferent Pathways

Sympathetic preganglionic neurons arise from the thoracolumbar spinal cord (Browning & Travagli, 2014) with cell bodies in the intermediolateral columns of the spinal cord (Furness et al., 2014). Stomach-innervating neurons typically arise from T5-T9 of the thoracic spine, while colon-innervating neurons typically arise from L2-L5 of the lumbar spine (Browning & Travagli, 2014). Sympathetic preganglionic neurons are cholinergic, resulting in the activation of postganglionic sympathetic neurons which have cell bodies in the prevertebral ganglia and innervate myenteric ganglia. This inhibits the excitatory effects of enteric neurons of gastric and intestinal muscle, slowing motility (Furness, Callaghan, Rivera, & Cho, 2014). One of many factors that can trigger this process is intestinofugal afferent neurons (IFANs), which release acetylcholine in the prevertebral ganglia in response to colonic distention (Szurszewski, Ermilov, & Miller, 2002). Another way that sympathetic efferent pathways can inhibit GI transit is by inhibiting movement by contracting sphincters (Payne et al., 2019).

1.11 Relationships between symptoms and autonomic dysfunction

1.11.1 Abdominal Pain

The nature of the location of visceral pain in the abdomen has shown to help predict which organ is affected. Visceral pain from the stomach, duodenum and gallbladder is typically localized in the epigastric area, visceral pain from the small intestine and appendix is typically localized in the umbilical region, and visceral pain from the colon is typically localized in the hypogastrium (Brown, 1942). Severe abdominal pain often accompanies GI dysmotility without distinct pathology and with unremarkable GI investigations. Smith-Edwards et al. proposed a model of parasympathetic spinal circuitry linking sensation and pain to gastrointestinal motility in mice (as expressed in Figure 7B in Smith-Edwards et al. 2019). They found that extrinsic primary afferent neurons, in addition to acting as sensory neurons, influence myenteric neuron activity through a parasympathetic spinal reflex, inducing smooth muscle contraction and GI motility (Smith-Edwards et al., 2019). If a primary insult effects afferent neurons or this spinal reflex, there may be resulting dysmotility and accompanying abdominal pain. This may be an explanation as to why GI dysmotility symptoms and abdominal pain are present in patients with unremarkable GI investigations (no overt organ damage nor clear pathology). Stimulation of the dorsal root ganglia via electrical stimulation resulted in the response of myenteric neurons to stimulate smooth muscle contraction, indicating that the neuromodulation of the DRG may evoke contractile activity to induce motility and simultaneously reduce accompanying pain via stimulation of extrinsic primary afferent neurons (Smith-Edwards et al., 2019). The anatomic features of different GI organ-related

abdominal pain raise the possibility of different levels of spinal innervation pathology leading to different GI dysmotility, which might be reversed by anatomy-guided neuromodulation.

FGIDs have a strong psychosocial component in the pathogenesis of GI symptoms. Corticotropin-releasing factor (CRF) pathways are involved in the stress response and dysregulation of CRF signaling systems have been found to contribute to stress-related alteration of GI function and visceral pain (Taché & Million, 2015) (Tache, Larauche, Yuan, & Million, 2018). Actions are mediated through the ANS and their site of action in the brain is at the paraventricular nucleus (PVN) of the hypothalamus, locus coeruleus complex (LC) and the dorsal motor nucleus (DMN). CRF receptor (CRF-R) signalling plays a key role in the stress response expressed by GI function, including inhibition of gastric acid secretion, the inhibition of gastric and small intestinal transit, stimulation of secretory-motor function, increased intestinal permeability and increased visceral hypersensitivity (Tache, Larauche, Yuan, & Million, 2018). CRF has different receptor types: CRF-R1, which stimulates colonic secreto-motor function and induces visceral hypersensitivity, and CRF-R2, which inhibits gastric motor function (Taché & Million, 2015). Activation of CRF-R1 has shown to induce stress-related visceral hypersensitivity or visceral hyperalgesia (Tache, Larauche, Yuan, & Million, 2018). Hypersensitivity and modulation of visceral pain occurs when CRF-R1 signaling occurs in the central nucleus of the amygdala (CeA), which has an abundance of CRF cell bodies and terminals, the bed nucleus stria terminalis, LC, and hippocampus (Gray, 1993). Vicario et al. (2011) found visceral hypersensitivity to occur in rats following stressful stimuli, as well as increased expression of CRF-R1 causing an increased number of mast cells in the colon mucosa (Vicario et al., 2012). Increased mast cells result in the disruption of the intestinal epithelial barrier, or intestinal permeability alteration, which has been found to be a feature in the development of visceral hypersensitivity (Larauche, 2012), resulting in high susceptibility of abdominal pain. Dysregulation of CRF signaling pathways may contribute to visceral abdominal pain experienced by some patients, leading to the potential for application of CRF-R1 antagonists for the treatment of stress-sensitive GI conditions and abdominal visceral hypersensitivity (Tache, Larauche, Yuan, & Million, 2018).

1.11.2 Gastroesophageal reflux

Animal and human studies have shown symptoms of dyspepsia, such as nausea and vomiting, to be associated with preceding decreases in lower esophageal sphincter (LES) pressure, or relaxation of the LES (Lang, 1990) (Lang, Sarna, & Dodds, 1993). Transient lower esophageal sphincter relaxations (TLESRs) are responsible for gastric reflux episodes, as seen in gastroesophageal reflux disease (GERD) (Mittal, Holloway, Penagini, Blackshaw, & Dent, 1995). Following the consumption of a meal in healthy

volunteers, there is an increase in the number of TLESRs and reflux episodes, positively correlated with an accompanying decrease in vagal activity, measured by cardiac vagal tone (CVT) (Kuo, Bravi, Marreddy, Aziz, & Sifrim, 2013). TLESRs are mediated by the vagus (Schaub, Ng, Kuo, Aziz, & Sifrim, 2014) and investigations in both healthy and GERD patients have found TLESRs to be triggered by gastric distention (Holloway, Hongo, Berger, & McCallum, 1985). Gastric distention is signaled by afferent fibres that project to the DMV, which contains vagal efferent cell bodies that project to the LES (Mittal, Holloway, Penagini, Blackshaw, & Dent, 1995), possibly mediating TLESRs, resulting in increases in TLESRs following a meal. Patients with symptoms of gastric reflux have shown to have an increased, excessive number of TLESRs compared to healthy controls (Mittal, Holloway, Penagini, Blackshaw, & Dent, 1995). These increases are significantly correlated with an increase in sympathetic tone and decrease in parasympathetic vagal tone (Kuo, Bravi, Marreddy, Aziz, & Sifrim, 2013). In patients who exhibit reflux episodes, such as patients with GERD, treatments, such as $GABA_B$ receptor agonists, are aimed to reduce the number of TLESRs (Grossi, Spezzaferro, Sacco, & Marzio, 2008).

1.11.3 Nausea

Symptoms of nausea have been associated with changes in the autonomic nervous system, specifically showing increased sympathetic activation and decreased parasympathetic activation (Cowings, Suter, Toscano, Kamiya, & Naifeh, 1986). When testing motion sickness in humans, Cowings et al., measured for changes in the ANS, finding increased sympathetic activation in all responses to motion sickness; including increased heart rate and ventilation. Gianaros et al. tested the relationship between motion-induced nausea and the ANS, using RSA as a parameter of parasympathetic autonomic activity. The study found that during nausea-inducing stimuli, RSA decreased over time as nausea prevalence increased (Gianaros et al., 2003). Decreases in RSA were significantly associated with higher severity of nausea symptoms, indicating the association between nausea and decreases in parasympathetic activity; a correlation previously seen in patients with chemotherapy-induced nausea (Gianaros et al., 2003). Relaxation of the fundus via the vagus nerve is the normal response after healthy individuals eat a meal. Significant, abnormal decreases in fundic tone, however, have shown to lead to the activation of gastric vagal afferents which stimulate neurons within the dorsal vagal complex and result in symptoms of nausea (Hornby, 2001). Gastric fundus tone, lower esophageal sphincter (LES) pressure and nausea are modulated by vagal and sympathetic pathways (Schaub et al., 2014). Schaub et al., conducted a study to assess gastroesophageal pressure and changes in the autonomic nervous system during nausea symptoms induced by visual motion. The study found a drop in pressure of the gastric fundus and the LES to be significantly associated with nausea. Nausea was also significantly associated with increased heart rate, suggesting increased sympathetic

tone, and decreased cardiac vagal tone (CVT), indicating decreased parasympathetic tone. Activation of vagal efferents stimulates parasympathetic activity, activating the excitatory cholinergic pathway and allowing for smooth muscle contraction (Browning & Travagli, 2014). This contraction allows for increased gastric fundus tone and pressure; therefore, we hypothesize that stimulation of vagal pathways should improve symptoms of nausea seen in patients with increased sympathetic activity. Consistently, vagal innervation might be disturbed by mechanical etiology such as spinal pathology-related nerve impingement or non-infectious chronic inflammation.

1.11.4 Bloating

Azpiroz & Malagelada suggest abdominal discomfort from gas retention to be due to uncoordinated intestinal motility (Azpiroz & Malagelada, 2005), on the basis that the perception of abdominal symptoms is highly dependent on a motor response (Serra et al., 2010). One possible reasoning for uncoordinated intestinal motility is lack of simultaneous pressure waves (SPWs) or lack of the coloanal reflex associated with SPWs; pancolonic SPWs start in the proximal colon and SPWs also occur when the high amplitude pressure wave (HAPW) ends in the transverse or descending colon. The generation of SPWs involves extrinsic autonomic pathways (Chen et al., 2018). Chen et al. conducted a study with 17 healthy volunteers, all occurrences of gas expulsion were associated with SPWs, as well as association with water and balloon expulsion during high-resolution colonic manometry with water filled catheters and a rectal balloon. Hence, SPWs were found to be the colonic motor pattern related to gas-expulsion. Haustral boundaries were not obliterated by SPWs, therefore allowing the expulsion of gas without the expulsion of solid content. These findings suggest that impairment of SPWs may lead to colonic dysmotility resulting in gas retention, particularly in patients with IBS (Serra et al., 2010). In the Chen et al., study (Chen et al., 2018), the interpretation was that when stimulating the rectum via bisacodyl or balloon distention, mechanoreceptors (both IGLE and IMA) detected stretch within the rectum, sending information to the sacral defecation centre, followed by brainstem centres. There is then the activation of the DMV where vagal nerves initiate activity in the proximal colon. In patients with symptoms of abdominal discomfort due to bloating and gas retention, stimulation of autonomic nerves should activate autonomic neural pathways, initiating SPW motor patterns in the proximal colon to propel gas and alleviate discomfort.

De Groat and Krier proposed, similar to most interpretations, that spinal nerve stimulation primarily affects sensory nerves so that any evoked motor patterns would be the result of the brain stem reacting to stimulated sensory activity (De Groat & Krier, 1978). Smith-Edwards et al. has found extrinsic primary afferent neurons to indirectly

influence myenteric neuron activity and smooth muscle contraction through the engagement of a parasympathetic spinal circuit, linking sensation and pain to motility in mice (Smith-Edwards et al., 2019).

1.11.5 Chronic Constipation

Sacral parasympathetic pathways innervate the distal gastrointestinal tract (including the left colon and the rectum), with sacral afferents projecting from pelvic and rectal nerves (Brookes et al., 2009) (Brookes et al., 2013). The stimulation of these afferent neurons, which have cell bodies in the dorsal root ganglia of the lumbo-sacral spinal cord, begin the initiation of a propulsive motor pattern. Activation of these autonomic pathways lead to the initiation of motor patterns in the distal colon by sacral parasympathetic nerves (Payne et al., 2019), leading to the stimulation of the colon, rectum and relaxation of the internal anal sphincter (Brookes et al., 2009). Parasympathetic neurons initiate motor patterns in the descending colon and inhibit internal anal sphincter activity (evoking relaxation) in preparation for defecation (Brookes et al., 2009). Dysfunction of the extrinsic autonomic pathways results in inability to successfully initiate a motor pattern, thus the inability to transport colonic content in the anal direction through spontaneous bowel movements, as seen in constipation.

The defecation reflex involves the activation of afferent neurons mediated by rectal stimulation (Brookes et al., 2009). Information is projected to Barrington's nucleus and the NTS (Valentino, Miselis, & Pavcovich, 1999). From Barrington's nucleus, information can be projected through the DMV to the vagus. This will initiate propulsive motor patterns in the proximal colon (HAPWs) that continue traveling in the anal direction under the control of sacral parasympathetic motor neurons (Valentino, Miselis, & Pavcovich, 1999). Autonomic dysfunction of the neural pathways contributing to the defecation reflex may result in insufficient initation or propulsion of a motor pattern (HAPW), resulting in difficulty producing a regular, complete bowel movement, thus chronic constipation (Devroede & Lamarche, 1974).

1.12 Transcutaneous Electrical Nerve Stimulation (TENS)

1.12.1 History of TENS

Electrical therapies for pain and treatment date back to Ancient Rome when Scibonius discovered that contact with torpedo fish, which produce an electric discharge, could provide symptomatic relief of pain (Stillings, 1975). Demonstrations from Galvani (Galvani, 1794) and Melzack & Wall (Melzack & Wall, 1965) eventually led to the increasing popularity of neuromodulation to treat conditions such as chronic pain. The first electrical stimulation device specifically designed for treatment was the Electreat, paving the way to what now is the modern-day TENS device (Gildenberg, 2006). In 1968,

Wall & Sweet developed an implantable stimulator for chronic pain via peripheral nerve stimulation (Sweet & Wepsic, 1968). Around the same time, Norman Shealy was responsible for the first documented stimulation of the dorsal column of the spinal cord to treat chronic pain and worked with engineer Thomas Mortimer to develop an implantable dorsal column stimulator (Shealy et al., 1967) and continued working on the development of neuromodulating devices. The first portable transcutaneous electrical nerve stimulation (TENS) device was developed by Medtronic in 1974 (Francis & Dingley, 2015), leading to the modern-day non-invasive, portable TENS devices. While traditionally used for treatment of chronic pain, TENS treatment for various conditions, such as GI dysmotility disorders, is increasingly being investigated.

1.12.2 TENS treatment for GI dysmotility

Several studies have TENS shown to be an effective therapy for treating colonic dysmotility, particularly constipation, in both children and adults (Veiga et al., 2013). Hutson et al investigated the use of TENS to treat slow-transit constipation in children whose motility issues exhibited an intrinsic disorder due to abnormalities of peristaltic function of the proximal colon. The study found that 1-6 months of daily treatment significantly improved long-term colonic motility in children (Hutson, Dughetti, Stathopoulos, & Southwell, 2015). While Hutson et al suggested the potential mechanism of stimulating autonomic nerve fibres and inhibiting sympathetic autonomic pathways, the involvement of the ANS was not tested or measured in the study.

Another study tested TENS as a treatment of idiopathic slow-transit constipation in adults, finding that TENS treatment three times per week for six weeks significantly increased the frequency of defecation in patients (Kim & Yi, 2014). Researchers suggested that the stimulation of sacral nerves via TENS placement over S2-S3 activated sacral parasympathetic efferents, however testing of the role of the ANS in this study has not been further investigated.

Leong et al investigated the long-term effects of TENS treatment in children with slow-transit constipation when treated 3 times per week for 1-2 months. Findings from questionnaires showed improvments in defecation frequency and wetness of stool in two thirds of patients, one third of which had significant effects lasting more than two years (Leong et al., 2011). Measurements of the autonomic nervous system were not taken in this study.

While many studies show TENS to be successful in treating symptoms of constipation, there are limited studies that specifically test the role of the autonomic nervous system in the treatment. HRV analysis of sacral nerve stimulation (SNS) treatments has shown improvements in constipation symptoms in rats to be associated with increased vagal activity and decreased sympathetic activity (Huang et al., 2019). Huang et al suggest this increase in parasympathetic vagal activity to be due to activation of the pelvic splanchnic nerves. ANS findings from SNS studies suggests sustained

effects on colonic dysmotility issues to be due to the neuromodulation of extrinsic autonomic pathways (Huang et al., 2019) (Veiga et al., 2013). TENS treatments aim to less-invasively stimulate afferent and efferent fibres via neuromodulation to improve motility. It was one of my main objectives to contribute to the evaluation of this treatment.

TENS treatment for colonic dysmotility has been studied, but TENS for the treatment of upper GI dysmotility symptoms does not have the same extent of research. Köklü et al. (2010) used vacuum electrodes for transcutaneous electric stimulation and applied them to the paravertebral area of T10-T12. After 12 treatment sessions over 4 weeks, 44 patients with functional dyspepsia showed reduced upper GI symptoms such as epigastric discomfort, pyrosis, bloating, early satiation, postprandial fullness, with improvements lasting at least one-month post-treatment (Köklü et al., 2010).

1.12.3 Mechanism of TENS for pain

The current from TENS that stimulates the nerve fibres results in action potentials in both directions from its origin point. Orthodromic impulses travel towards the axon terminal (normal direction of natural impulses), while antidromic impulses travel towards the neuronal cell body (opposite direction of natural impulses). The antidromic impulses generated by TENS activate peripheral nerves, ultimately generating nerve impulses which collide and extinguish afferent impulses travelling from peripheral structures to the CNS. This peripheral blockade of afferent impulses, such as those stimulated from nociceptive events (Johnson, 2014), is more likely to occur when activating A-δ fibres, as seen in acupuncture-like TENS with low frequency-high intensity stimulation (Johnson, 2007).

Acupuncture-like TENS, or TENS treatment where stimulation parameters involve low pulse frequency and high intensity, aims to stimulate myelinated small-diameter, high threshold peripheral afferents (A-δ) to activate extra-segmental descending pain inhibitory pathways (Johnson, 2007). Small-diameter, high threshold peripheral afferents conduct nerve impulses related to transduction of pressure and noxious stimuli, and some are mechanoreceptors, activated by muscle contractions (Johnson, 2014). When they enter the spinal cord, muscle afferents branch forming pre- and post-synaptic connections with central nervous system transmission neurones in laminae of the spinal cord. When small-diameter afferents are stimulated by TENS, this results in the excitation of CNS transmission neurons involved in ascending pathways which synapse in regions of the brain such as the periaqueductal grey in the mid brain and nucleus raphe magnus (Johnson, 2014). These areas of the brain are then involved in descending pain-inhibitory pathways. This forms a feedback loop to the spinal cord, which aids in the prevention of future transmission of noxious sensory information.

TENS has shown to have long-lasting effects beyond the time of stimulation. Sandkühler et al. (1997) found that low-frequency stimulation of A-δ fibres in rats had long-term depression effects of post-synaptic potentials in afferent nerve fibres at least 2

hours past stimulation time. Long-term effects resulted from continuous or repetitive stimulation, suggested to be due to mechanisms such as adaptation, habituation, receptor desensitization or feedback inhibition (Sandkühler, Chen, Cheng, & Randić, 1997).

1.12.4 Mechanism of TENS for GI dysmotility

Electrical stimulation of autonomic pathways to treat colonic dysmotility symptoms may involve the activation parasympathetic pathways and inhibition of sympathetic pathways to induce GI motility. Electrical impulses are sent to nerves in GI organs via TENS to bring neural membrane potentials to threshold, generating action potentials and stimulating a neuronal circuitry which may be involved in GI motility, for example, the generation of a HAPW. TENS has shown to have long-lasting effects on GI dysmotility symptoms (Leong et al., 2011) (Hutson et al., 2015), therefore the mechanism behind TENS treatment cannot exclusively be evoking a motor contraction. Instead, electrical stimulation may involve the stimulation of a neural circuitry. If a neural circuitry is irregular or abnormal (in a state of allostasis), such as the one which generates a HAPW in some patients with colonic motility disorders, continuous stimulation of this circuitry may regulate its activity back to its homeostatic zone, resulting in long-lasting effects beyond treatment time.

TENS treatment on the thoracic spine is likely to stimulate nerves in the dorsal root ganglia (DRG) of the thoracic spinal cord. The DRG is comprised of afferent neurons travelling along sympathetic and somatic fibres; as previously discussed, afferent neurons are responsible for the mediation of nociceptive events in the upper GI tract (Figure 1.2) (Deer et al., 2019). Stimulation of the DRG via neuromodulation treatment has shown to affect the transmission of sensory pain signals from the periphery to the CNS (Deer et al., 2019). Treatment stimulates afferent pathways in the DRG, possibly reducing responsiveness to nociceptive and neuropathic stimuli (Xie, Strong, Li, & Zhang, 2007). While exact mechanisms of TENS stimulation are unknown, TENS treatment of the thoracic spine may have a therapeutic effect on GI dysmotility symptoms due to stimulation of the sensory pathways within the DRG.

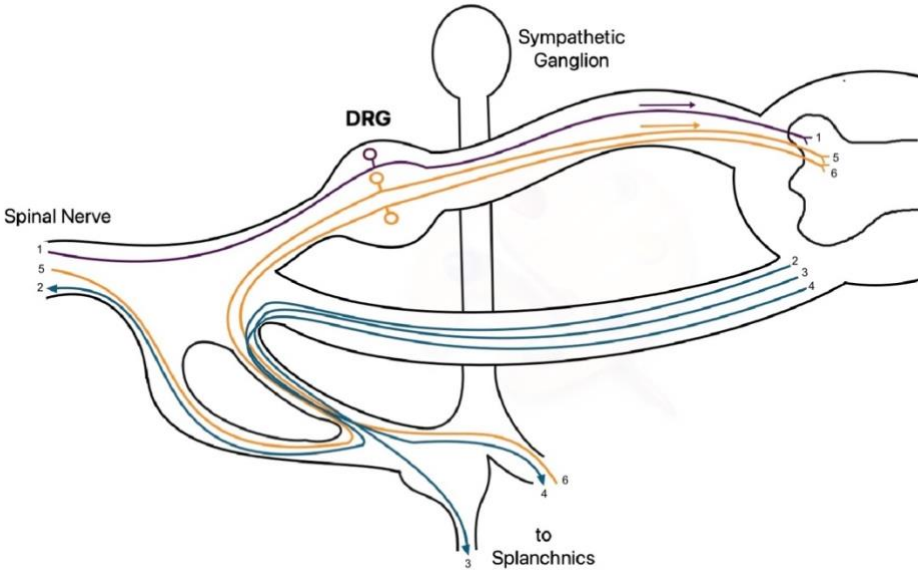

Figure 1.2 Schematic representation of the electrical pulses running to the dorsal root ganglia and to the dorsal horn.
Schematic representation of the electrical pulses running to the DRG and to the dorsal horn. Somatic afferent fibers (1) and afferent nerve fibers of the ANS (5, 6), run through the DRG, which act to block, propagate or filter potentials from the periphery. Sympathetic efferent fibers (2, 3, 4) run from the anterior nerve root to the spinal nerve and to splanchnic nerves.

2 Relationships between spinal conditions and GI dysmotility

2.1 Abstract

The pathophysiology of complex gastrointestinal (GI) dysmotility is poorly understood, resulting in challenges in providing a pathophysiological diagnosis and limited effective treatment options. The overlapping abnormalities of gastroenterology and neurology is increasingly realized to be critically important in the pathogenesis of complex gastrointestinal dysmotility, usually leading to significant impairment of GI function, such as poor oral food intake requiring surgical interventions and/or home nutritional support. The relationship between thoracolumbar spinal pathology and GI dysmotility has not been thoroughly studied. Given the importance of thoracolumbar spine innervation to the gut, specifically the sympathetic control on gut motility, further understanding of the clinical relevance of thoracolumbar spine pathology and its underlying pathophysiology in complex GI dysmotility may improve patients' outcomes and reduce the impact on the health care system. This study identified GI symptoms, such as epigastric tightness, postprandial hiccups, and vomiting, needing further investigation as symptoms indicative of spinal pathology within thoracic and lumbar regions of the spine.

2.2 Introduction

Complex gastrointestinal (GI) dysmotility has been challenging and complex to diagnose, and the pathophysiology of many patients is poorly understood, therefore, there are limited effective treatment options. Many patients have unremarkable GI investigations without a clear GI diagnosis other than 'functional GI disorder'. Symptoms can be severe but often non-specific, such as severe postprandial abdominal pain requiring ER visits and difficulty of oral food intake requiring surgical interventions and home-based nutritional support. Patients usually have frequent hospitalizations with a lack of effective pharmacological treatments or dietary/lifestyle modifications.

A study from our laboratory (Ali, Liu, Chen, & Huizinga, 2021) found that patients with refractory colonic dysmotility showed high sympathetic tone and reactivity, suggesting that sympathetic dysregulation plays an important role in refractory constipation. The aim of our research is to focus on ANS modulation as the primary treatment, not surgical removal of the colon. These studies have led to the hypothesis that complex GI dysmotility involving upper GI may involve sympathetic dysregulation as a primary cause.

The extrinsic autonomic innervation of the GI tract, which mainly arises from the thoracolumbar spine, plays an integral role in gastrointestinal transit and the process of

digestion (Browning & Travagli, 2014). The sympathetic innervation of the GI tract arises from T5-L2 of the thoracolumbar spinal cord, while the parasympathetic innervation arises from the vagus and sacral (S1-S5) spinal nerves. The greater splanchnic nerve branches from T5-T9 via thoracic sympathetic ganglia and plays a role in the inhibition of motility and secretions of the duodenum, stomach and distal esophagus (Sidawy & Perler, 2018). The greater splanchnic nerve is also responsible for the innervation of the spleen capsule to allow for the transmission of splenic pain (McCausland & Sajjad, 2021). Lesser splanchnic nerves from T10-T11 innervate the superior mesenteric ganglion to provide sympathetic innervation and inhibit motility in the jejunum, ileum, ascending and transverse colon (McCausland & Sajjad, 2021). The least splanchnic nerve arises from T12 sympathetic ganglia and contributes to the sympathetic innervation of the renal plexus (McCausland & Sajjad, 2021). Lumbar splanchnic nerves arise from L1-L2 of the sympathetic chain and terminate in the inferior mesenteric and hypogastric ganglia. They are responsible for the inhibition of smooth muscle contraction of the colon via sympathetic innervation.

The hypogastric nerve arises from T12-L3 of the thoracolumbar spinal cord, carrying sympathetic inputs from T12-L3 to the inferior hypogastric plexus (Yoham & Bordoni, 2022). The inferior hypogastric plexus plays a role in the innervation of the rectum and includes sympathetic fibres from the superior hypogastric plexus (via the hypogastric nerve), sacral splanchnic nerves from T10-L2 of the sympathetic trunk, pelvic splanchnic nerves and afferent visceral fibres from the pelvic viscera (Yoham & Bordoni, 2022). The hypogastric plexus contains both parasympathetic and sympathetic nerve fibres. The main function of this plexus is to supply the pelvic and perineal organs.

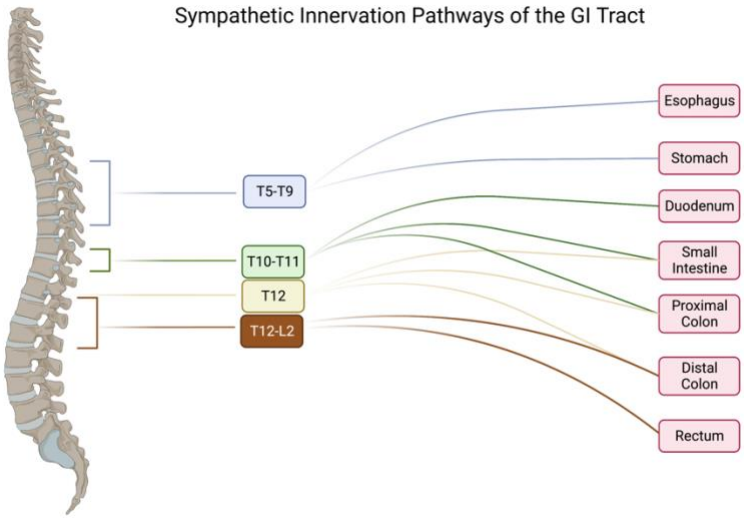

Figure 2.1 Sympathetic innervation of the gastrointestinal tract.
Sympathetic innervation of the gut arising from T5-L2 of the thoracolumbar spinal cord. Our hypothesis outlines that disruptions to these autonomic spinal pathways in the thoracolumbar region of the spine may contribute to the pathology of motility symptoms in corresponding GI organs.

Spinal pathology such as degenerative disc or vertebral changes, stenosis, and scoliosis is common in adults. It is also common that patients with complex GI dysmotility present with a history

of spinal pathology or spinal injury, warranting a study of the relationships between GI pathophysiology and spinal nerve pathology. Degenerative changes to vertebrae and/or intervertebral discs can cause impact on spinal nerves, such as stenosis and related symptoms. Scoliosis is defined as a lateral spinal curve >10° (Spivak & Connolly, 2006) and can be idiopathic, however is most commonly seen in adults as degenerative. Idiopathic scoliosis is most often seen in adolescence, in which rapid periods of growth can result in the progression of significant spinal deformities (Bettany-Saltikov, Weiss, Chockalingam, Kandasamy, & Arnell, 2016). Severe idiopathic scoliosis may be accompanied by symptoms of cardiopulmonary and gastrointestinal dysfunction; severe scoliosis at the thoracic level (≥40°) in particular has shown to have impact on pulmonary function (Weinstein, Zavala, & Ponseti, 1981). Degenerative scoliosis often begins with the intervertebral discs and facet joints degenerating asymmetrically, causing an imbalance in the loading of the spine and the progression of a deformity (Aebi, 2005). It is common for degenerative, or “de novo” scoliosis to be accompanied by spinal stenosis, involving the narrowing of the spinal canal and the potential compression and/or disruption of the spinal nerves (Aebi, 2005). Injury to the spinal cord has commonly shown to result in colonic dysmotility and other bowel dysfunctions (Vallès, Rodríguez, Borau, & Mearin, 2009), warranting the study of the relation of other spinal pathology on GI function.

The overlapping symptoms of gastroenterology and neurology (‘neurogastroenterology’) in clinical settings are largely due to the involvement of the autonomic nervous system in digestive processes, and this should encourage the diagnosis process of GI dysmotility not to stop at only gastroenterology investigations. Patients with complex GI dysmotility usually received 1 or more endoscopic procedures, which mostly are unremarkable. Clinical guidelines have also been limited to GI perspectives, leading to the absence of critical clinical reasoning on differential diagnosis. Disorders or dysfunction of the autonomic nervous system often results in manifestations of GI dysmotility, hence knowledge of neurological processes, as well as neurological investigations should be standard in the practice of gastroenterology (Jain, 2000). That is why we use the term of “Neurogastroenterology”. Investigations of the relationship between neurology and gastroenterology have shown that chronic intestinal pseudo-obstruction has neurological pathology (dysfunction or disruption of the enteric nervous system), hence the incorporation of neurological investigations should have an important role in clinical gastroenterology practice (Mathias & Clench, 1995).

The aim of this study was to investigate the relationships between symptoms of GI dysmotility in complex GI dysmotility patients and their thoracolumbar spinal pathology, including scoliosis and other spinal conditions. These were patients from Dr. Chen’s clinic who did not have a straightforward diagnosis, including a clear primary diagnosis of severe GI dysmotility, including severe constipation or fecal incontinence and/or upper GI

organ dysmotility, and had a spinal condition. We refer to the patient group discussed here as having “complex GI dysmotility”.

Specific Objectives:

- To investigate the clinical features of complex GI dysmotility via a self-report questionnaire designed by our group
- To determine the relationship between thoracic and lumbar spine pathology and GI dysmotility symptoms in patients with scoliosis and other spinal conditions

2.3 Methods

Subjects

Thirty-nine patients with complex GI dysmotility (18 to 77 years old; 35 females and 4 males) from McMaster University Digestive Disease outpatient clinic were recruited. These were patients from Dr. Chen’s clinic who did not have a straightforward diagnosis nor pathology, including a primary diagnosis of severe constipation or fecal incontinence and/or dysmotility of upper GI organs, and had a spinal condition. We also excluded patients with obvious cardiac autonomic dysfunctions to particularly investigate spinal pathology-induced autonomic dysfunctions.

Patients’ diagnosis was determined by Rome IV diagnostic criteria for FGIDs, and their spinal pathology was diagnosed by diagnostic imaging of the spine, such as X-ray, MRI or CT scans, including scoliosis, degenerative changes, herniated disc, spinal stenosis and post trauma (e.g., motor vehicle accidents (MVAs), falls, sport-related injuries). Four groups of patients were studied based on the location of their spinal pathology: T5-T9 (the greater splanchnic nerves origin), T10-L2 (the lesser splanchnic nerves origin) and L2-L5 (the lumbar spine) pathology, and T10-L2 scoliosis. Patients were then sub-grouped based on the type of spinal pathology, such as scoliosis, disc bulging, disc herniation, etc. T10-L2 scoliosis was studied separately to investigate its specific clinical profile.

Symptoms data collection

Collection of patient symptom information was completed through a combination of a questionnaire outlining GI symptoms and quality of life, medical history, and direct communication with patients.

An online, self-report symptom questionnaire was developed to assess GI dysmotility symptoms of both upper and lower GI tracts, as well as neurological symptoms, in large part because of COVID-19 restrictions. The questionnaire was organized anatomically, such as head symptoms, chest symptoms, mouth/throat symptoms, abdominal symptoms, etc. Patients were given access to the questionnaire to complete at-home, but also given the option to complete with the researcher via phone

call if preferred. All patients indicated that the questionnaire was completed in the stage "Before TENS" (section A3 of the questionnaire – see Appendix).

Symptom questionnaire scoring

Patient symptom scores were determined as follows related to the GI questionnaire.

If a symptom occurred infrequently (<30% of the time), it is scored as 1.
If the symptom occurred frequently (30-60% of the time), it is scored as 2.
If the symptom occurred very frequently (>60% of the time), it is scored as 3.

If the symptom was mild severity (1-3 pain scale out of 10), it is scored 1.
If the symptom was moderate severity (4-6 pain scale out of 10), it is scored 2.
If the symptom was severe (7-8 pain scale out of 10), it is scored 3.
If the symptom was very severe (9-10 pain scale out of 10), it is scored 4.

To score each individual symptom, the product of the scored frequency and severity of that particular symptom was calculated. The product of these scores is the score of the symptom. For example, if the frequency of heartburn is 'Frequent' (score of 2) and the severity is 'Severe' (score of 3), the overall score for heartburn is 6. For each section of the questionnaire (Head symptoms, Chest symptoms, Abdominal Symptoms…etc.), the sum of each individually scored symptom (as calculated above) was calculated to determine the total score for that section. For example, if the score of heartburn is 6 and the score of spontaneous hiccups is 4, the total score for Chest Symptoms is 10. We considered a symptom score of 1-3 to be mild, 4-5 to be moderate, 6-8 to be severe and 9-12 to be very severe. The GI dysmotility questionnaire was attached in the appendix.

2.4 Data analysis

The distribution of symptom severity data collected from patients via self-report questionnaire is presented and analyzed via boxplot. Boxplots were constructed to allow for comparative analysis on the differences in the distribution of reported severity of symptoms for each spinal group. In the boxplots, the bottom line (Q1) represents the 25th percentile (first quartile) and top line (Q3) represents the 75th percentile (third quartile) (Figure 2.2). This makes up the interquartile range, indicating that 50% of patient severity data is within this range. The thick line within the box is the median (Q2), indicating that 50% of patients within the group report severity scores *higher* than the median. The upper and lower whiskers show the distribution of patient data to the maximum and minimum data point within 1.5 box heights from the top and bottom of the box, respectively. Any

data points outside of the upper and lower whiskers indicate the presence of an outlier. The smaller the interquartile range, the smaller the distribution of the data in that group is.

Correlation analysis was performed for each symptom and spinal group, with correlation coefficients presented in a correlation matrix, with the aim of determining potential symptoms correlated with a specific spinal group. Correlation analysis was also performed on multiple symptoms and spinal groups to determine correlation between the presentation of multiple symptoms and each spinal group.

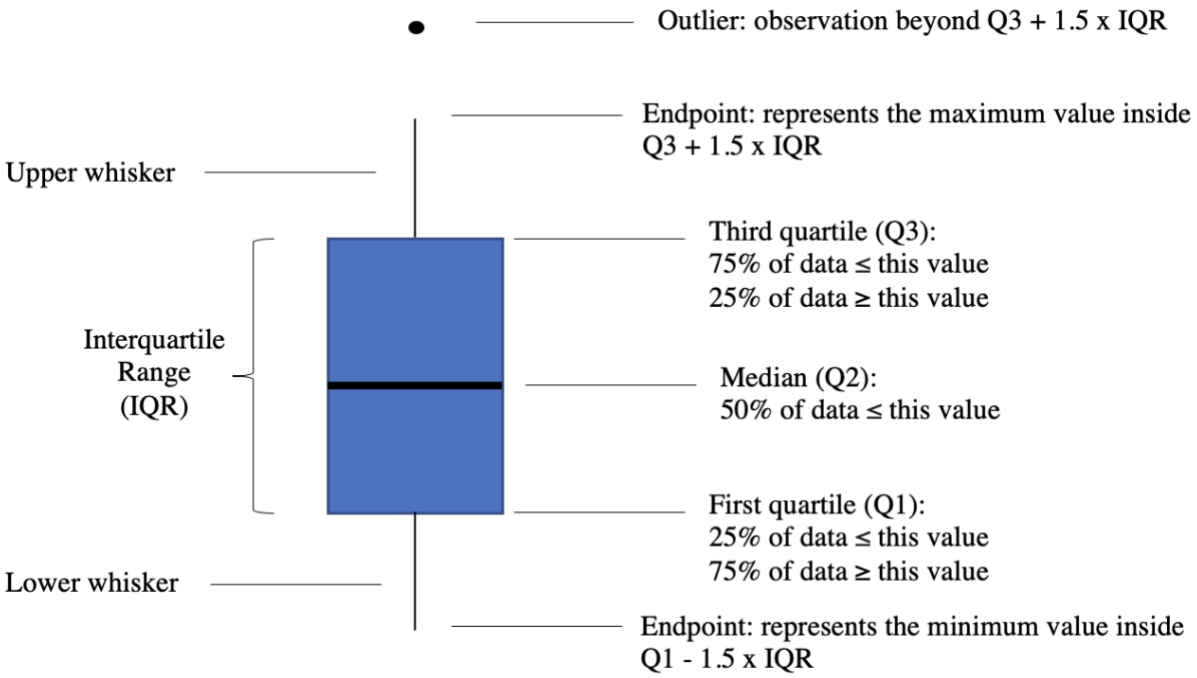

Figure 2.2 Boxplot reading tool used during the analysis of the distribution of symptom severity data.

2.5 Results

Patients with gastroparesis

Of the thirty-nine patients involved in the study, thirteen patients (33%) had previously undergone a delayed gastric emptying study to test for gastroparesis, while 67% had not undergone any test. In the T10-L2 scoliosis group, five patients had previously had a gastric emptying study; 2 patients having positive results (confirmed gastroparesis) and 3 patients having negative results (no gastroparesis).

Table 2.1 Results of delayed gastric emptying studies to confirm a diagnosis of gastroparesis in all spinal groups.

Delayed Gastric Emptying Study	Positive N (%)	Negative N (%)	No Test N (%)
T3-T9	2 (22%)	0	7 (78%)
T10-L2 Scoliosis	2 (13%)	3 (20%)	10 (67%)
T10-L2 Non-scoliosis	2 (33%)	0	4 (67%)
L2-L5	4 (44%)	0	5 (56%)
All spinal groups	**10 (26%)**	**3 (8%)**	**26 (67%)**

Symptoms associated with T3-T9 spinal pathology

A total of nine patients had spinal pathology located at the T3-T9 region, consisting of degenerative conditions such as stenosis (n=3), disc bulging (n=1) disc herniation (n=1), disc misalignment (n=1), scoliosis (n=1), kyphosis (n=1) and Scheuermann's kyphosis (n=1). Common symptoms were nausea, postprandial abdominal pain, postprandial hiccups, regurgitation, vomiting, and abdominal gurgling (Fig. 2.3).

Reported severity scores of postprandial hiccups in the T3-T9 group reported higher median severity (6 (*severe*)) than all other spinal groups (all other spinal groups with median of 0), indicating that the T3-T9 group had not only higher prevalence of postprandial hiccups, but also higher reported frequency and severity of the symptom (Fig. 2.4). Reported severity scores of vomiting was also reported to be higher in the T3-T9 group, with the interquartile range of vomiting reaching a severity over 7.5 (severe), while all other groups had upper whiskers no higher than a severity of 4 (mild) (Fig. 2.5). This indicates that the T3-T9 group not only had the highest prevalence of reports of vomiting, but also more severe vomiting compared to all other spinal groups.

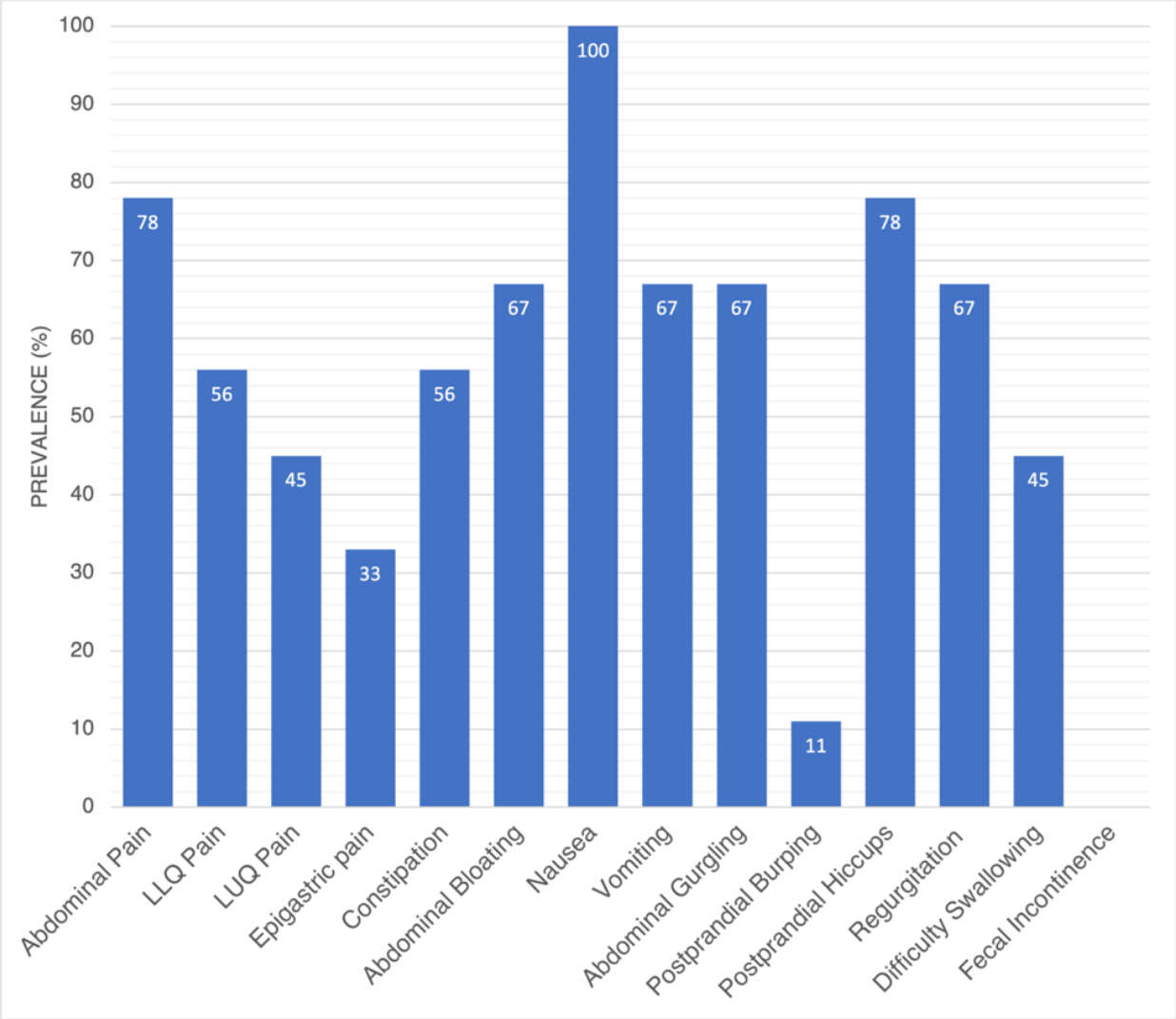

Figure 2.3 Prevalence of dominant GI symptoms reported by patients with spinal pathology located at the T3-T9 level (n=9).
Patients' spinal pathology included stenosis (n=3), disc bulging (n=1) disc herniation (n=1), disc misalignment (n=1), scoliosis (n=1), kyphosis (n=1) and Scheuermann's kyphosis (n=1). Most prevalence GI symptoms reported by patients include severe postprandial abdominal pain, nausea, abdominal bloating, postprandial hiccups, vomiting, abdominal gurgling and regurgitation. The number inside each bar reflects the prevalence of patients exhibiting each specific symptom (percentage).

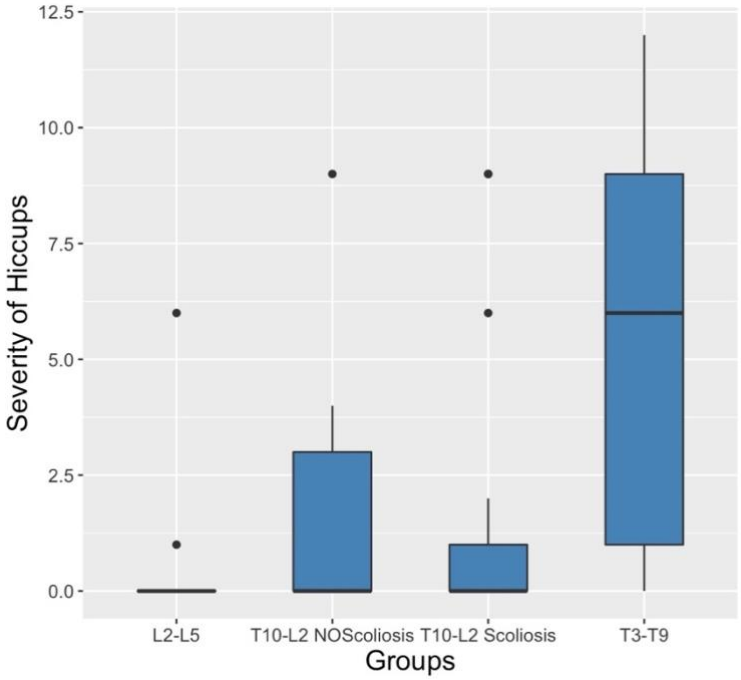

Figure 2.4 Boxplot of symptom severity scores of postprandial hiccups indicating highest severity in T3-T9 group.
Boxplot outlines distribution of postprandial hiccup severity scores for the 4 groups: L2-L5 group (n=3/9), T10-L2 non-scoliosis group (n=2/6), T10-L2 group (n=4/15), and T3-T9 condition (n=7/9). The severity median of the T3-T9 group was 6, indicating that 50% of the T3-T9 group reported severity scores of 6 or higher (severe). All other groups had a median of 0, with distribution no higher than 2 (mild) in the T10-L2 scoliosis group and 4 (moderate) in the T10-L2 non-scoliosis group.

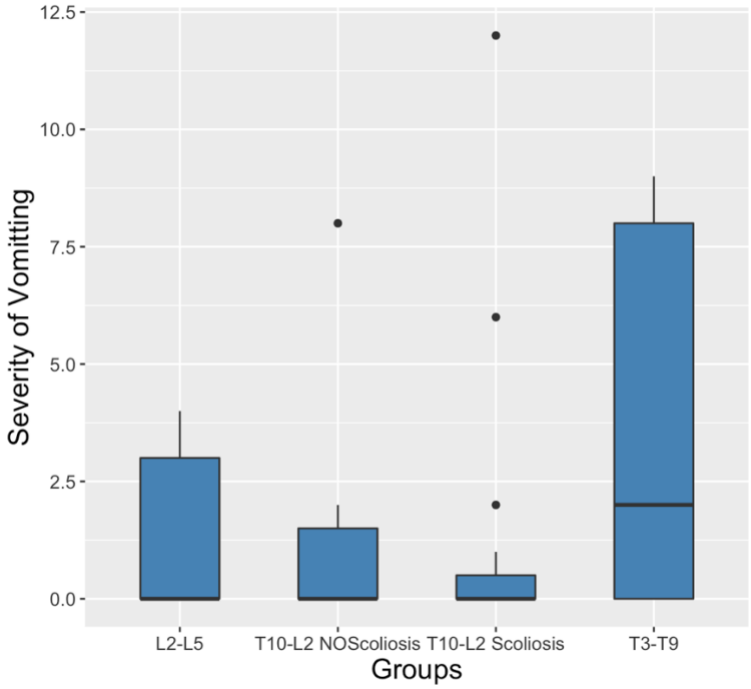

Figure 2.5 Boxplot of symptom severity scores of vomiting (> 6 hours after a meal) indicating highest severity in the T3-T9 group.
Boxplot outlines the distribution of vomiting severity for the four spinal condition groups: L2-L5 group (n=3/9), T10-L2 non-scoliosis group (n=2/6), T10-L2 scoliosis group (n=4/15), and T3-T9 group (n=6/9). Severity median was highest in the T3-T9 group at 2 (mild), while the interquartile range extended across the highest scores in the T3-T9 group (25^{th}-75^{th} percentile severity between 2 and 8 (mild and severe, respectively)). L2-L5, T10-L2 non-scoliosis and T10-L2 scoliosis groups each had severity medians of 0 and all other ranges and upper whiskers no higher than 4 (mild), indicating that the reports of vomiting were most severe in the T3-T9 group.

Symptoms associated with scoliosis of T10-L2

A total of fifteen patients had scoliosis at the T10-L2 thoracolumbar region of the spine. All patients had mild-curve scoliosis (Cobb angle 10°-25°). The most dominant symptoms reported by patients include severe postprandial abdominal pain, nausea, constipation, and abdominal bloating (Fig. 2.6).

The severity of reported postprandial abdominal pain was generally more severe in the T10-L2 scoliosis group, with the 25th-75th percentile being above a score of 8.5 (severe), however the T10-L2 non-scoliosis and L2-L5 groups also often reported severe postprandial abdominal pain (Fig. 2.11). The severity of sudden-onset constipation was reported as most severe in the T10-L2 scoliosis group, with 50% of the group reporting constipation severity to be a 9 or above (very severe) (Fig. 2.7). The interquartile range of the T10-L2 scoliosis group was also the highest of all spinal groups, indicating that the 25th-75th percentile reports severity scores between 2.5 (mild) to 9 (very severe).

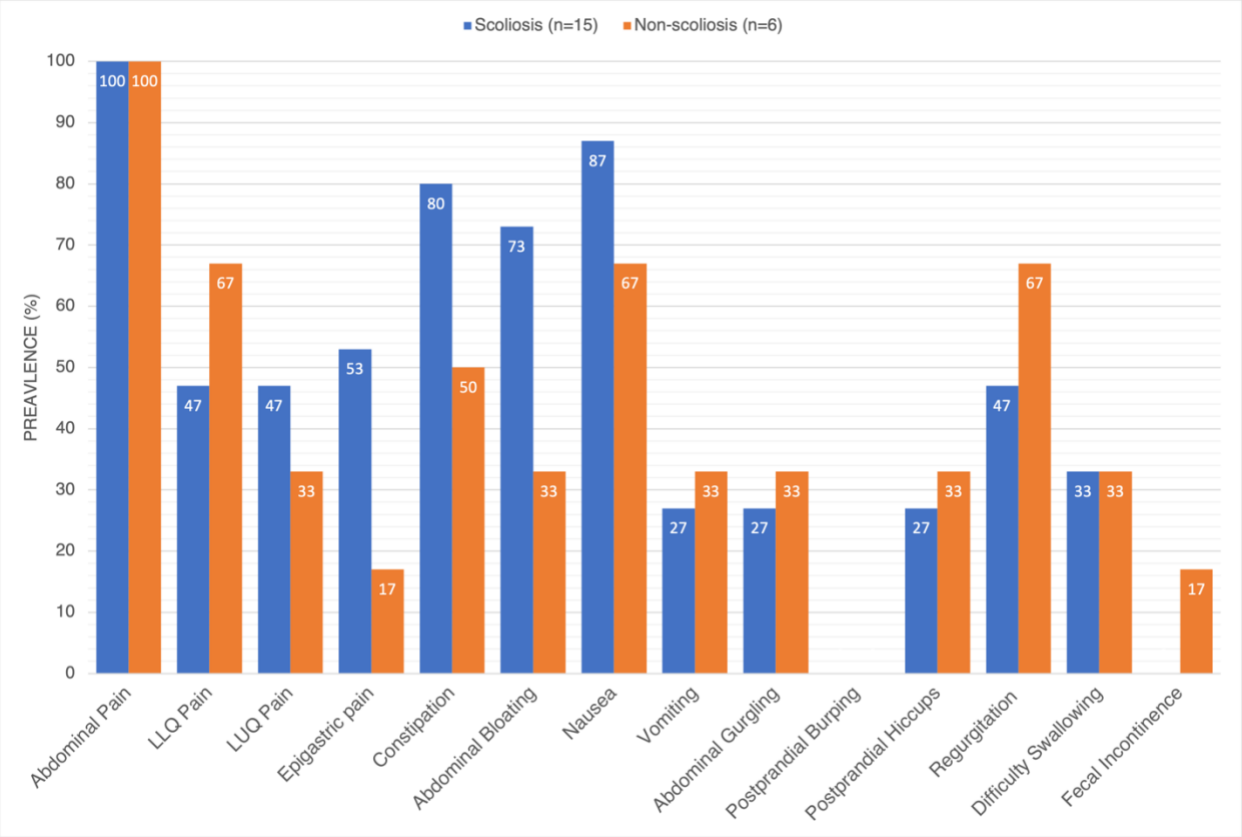

Figure 2.6 Prevalence of dominant GI symptoms reported by patients with T10-L2 scoliosis versus T10-L2 non-scoliosis pathology.
Most prevalent GI symptoms reported by scoliosis patients (blue, n=15) include severe postprandial abdominal pain, nausea, constipation, and abdominal bloating. Most prevalent GI symptoms reported by patients with other spinal conditions in at the T10-L2 level (orange, n=6) include severe postprandial abdominal pain, pain in the left lower quadrant, nausea and regurgitation.

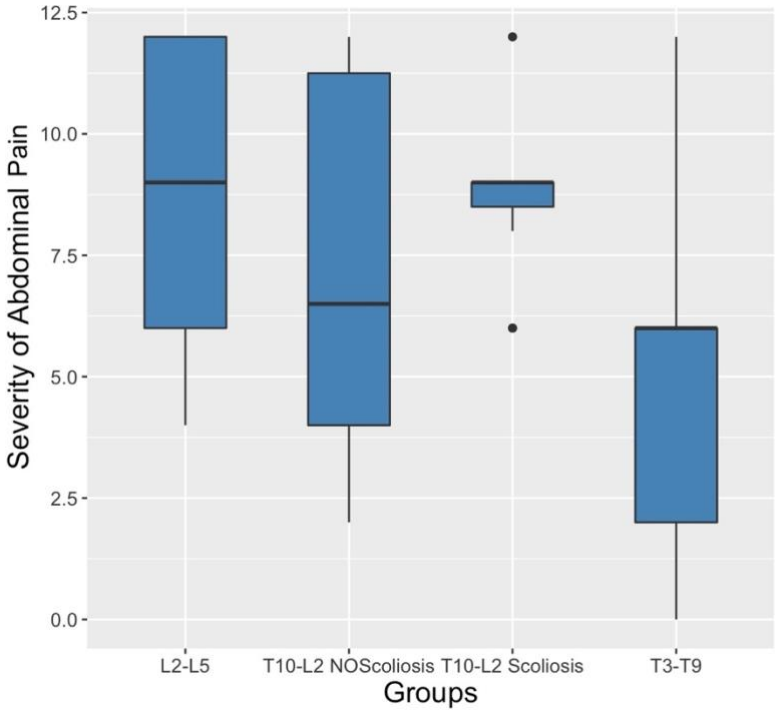

Figure 2.7 Boxplot of symptom severity scores of postprandial abdominal pain indicating highest severity in T10-L2 scoliosis group, followed by the L2-L5 and T10-L2 non-scoliosis group.
Boxplot outlines the distribution of postprandial abdominal pain severity for the four spinal condition groups: L2-L5 condition (n=8/9), T10-L2 non-scoliosis condition (n=6/6), T10-L2 scoliosis (n=15/15), and T3-T9 condition (n=7/9). The interquartile range of the scoliosis group was narrow, above a severity of 8.5 (severe), with the median above 8.75 (severe). The severity of postprandial abdominal pain reported by other spinal groups had broader interquartile ranges but also had reports of the symptom. The T3-T9 group had lower reported severity scores of postprandial abdominal pain.

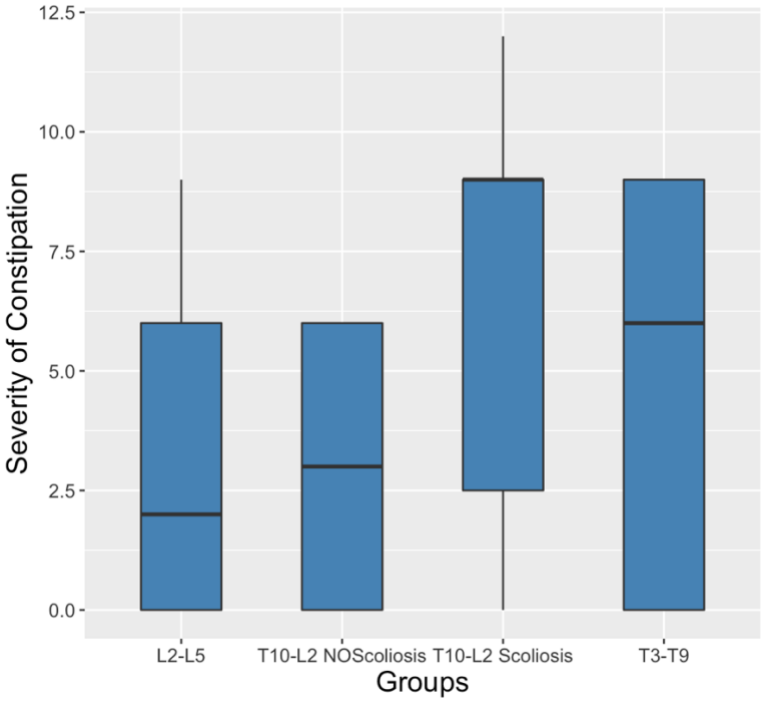

Figure 2.8 Boxplot of symptom severity scores of sudden onset constipation indicating highest severity in the T10-L2 group.
Boxplot outlines the distribution of constipation severity for the four spinal condition groups: L2-L5 condition (n=5/9), T10-L2 non-scoliosis condition (n=3/6), T10-L2 scoliosis (n=12/15), and T3-T9 condition (n=5/9). The severity median of the T10-L2 scoliosis group was 9 (very severe), higher than the severity median of all other spinal groups. The T3-T9 group has a severity median of 6 (severe), T10-L2 non-scoliosis group has a severity median of 3 (mild), and L2-L5 group has a severity median of 2 (mild).

Symptoms associated with other spinal conditions (non-scoliosis) of T10-L2

A total of six patients had other spinal conditions (non-scoliosis) in the T10-L2 region of the thoracolumbar spine, including degenerative spinal conditions such as disc herniation (n=1) and narrowing of the spinal canal (n=1), kyphosis (n=2), vertebral hemangioma (n=1) and Tarlov cyst (n=1).

Patients reported most dominant GI symptoms to be severe postprandial abdominal pain, particularly in the left lower quadrant of the abdomen, nausea, and regurgitation (Fig. 2.6). Each of these six patients also exhibited spinal conditions of other regions of the spine, such as the cervical and/or lumbar spine.

Differences in symptoms associated with scoliosis versus other spinal conditions (non-scoliosis) of T10-L2

The T10-L2 scoliosis and T10-L2 non-scoliosis groups showed some similarities in dominant symptoms, such as severe postprandial abdominal pain (100% and 100%, respectively) and nausea (87% and 67%, respectively) (Fig. 2.6).

Main differences between the scoliosis and non-scoliosis group include higher prevalence of left lower quadrant abdominal pain (67% in non-scoliosis group; 47% in scoliosis group) and regurgitation (67% in non-scoliosis group; 47% in scoliosis group) in the non-scoliosis group, and higher prevalence of constipation (80% in scoliosis group; 50% in non-scoliosis group), abdominal bloating (73% in scoliosis group; 33% in non-scoliosis group) and epigastric pain/tightness (53% in the scoliosis group; 17% in the non-scoliosis group) seen in the scoliosis group (Fig. 2.6).

Symptoms associated with spinal conditions of L2-L5

A total of nine patients had spinal conditions in the L2-L5 region of the lumbar spine, including stenosis (n=2), disc bulging or herniation (n=3), disc space narrowing (n=1), soft tissue edema (n=1) and general degenerative changes (n=2). The most dominant GI symptoms reported by patients include severe postprandial abdominal pain, abdominal bloating, constipation and nausea (Fig. 2.9).

Excluding L2-L5 spinal patients who also had spinal conditions in other regions of the spine (cervical or thoracic) (n=3), those only with spinal conditions in the L2-L5 regions report higher accounts of constipation and abdominal bloating, and lower accounts of nausea (Fig. 2.10).

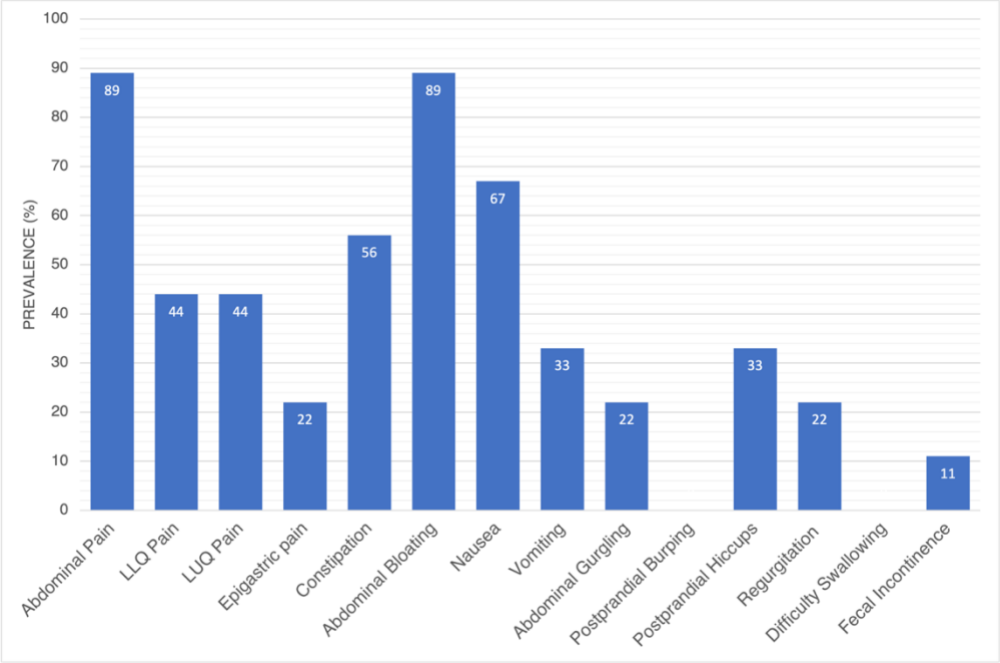

Figure 2.9 Prevalence of dominant GI symptoms reported by patients with spinal pathology located at the L2-L5 level (n=9). Most prevalent GI symptoms reported by L2-L5 spinal patients include severe postprandial abdominal pain, abdominal bloating, nausea and constipation.

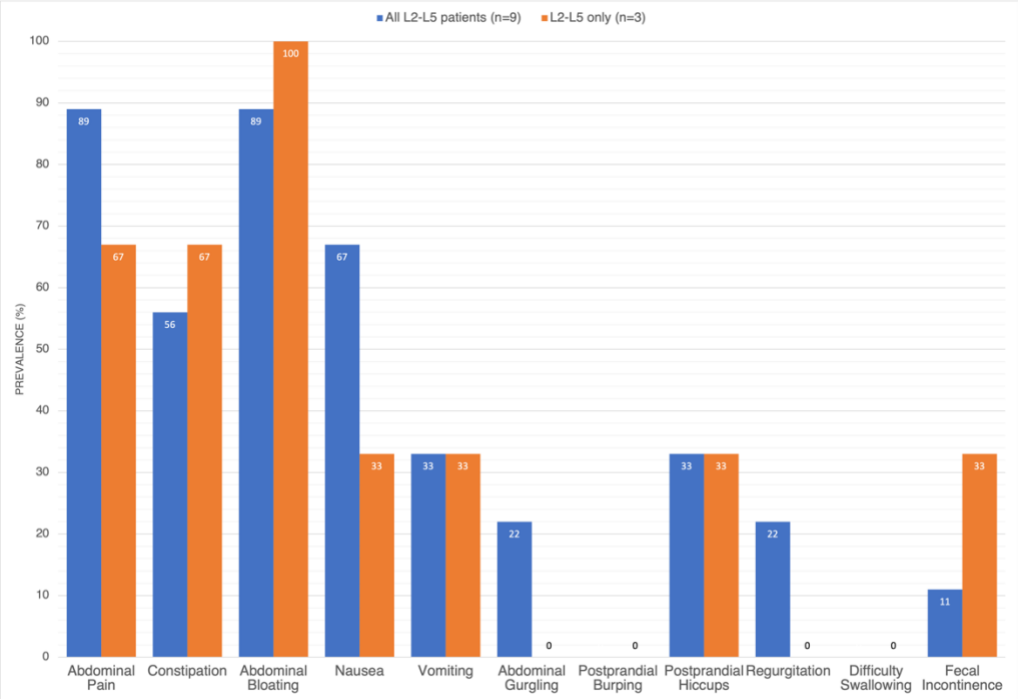

Figure 2.10 Prevalence of dominant GI symptoms reported by all L2-L5 spinal patients versus subgroup of patients whose only spinal condition is located at L2-L5. Abdominal bloating and constipation are slightly higher reported by patients only diagnosed with L2-L5 conditions (orange, n=3), while nausea and postprandial abdominal pain is more reported by patients with additional conditions in other regions of the spine, such as the cervical and/or thoracic spine (blue, n=9).

Differences in dominant symptoms among all spinal groups

In the comparison of the prevalence of dominant symptoms exhibited by patients based on spinal location group, all spinal groups showed significant reports of severe postprandial abdominal pain (T3-T9 group at 78%; T10-L2 scoliosis group at 100%; T10-L2 non-scoliosis group at 100%; L2-L5 group at 89%) (Fig. 2.11). Postprandial abdominal pain was most highly correlated with the T10-L2 scoliosis group (Fig. 2.20). The reported severity of postprandial abdominal pain was also generally more severe in the T10-L2 scoliosis group, with 75% of the group reporting a score of at least 8.5 (severe). The T10-

L2 non-scoliosis group and L2-L5 group both also showed significant reports of severe postprandial abdominal pain, with 50% of the L2-L5 group reporting severity of at least 9 (very severe) and 50% of the T10-L2 non-scoliosis group reporting severity of at least 6.5 (severe) (Fig. 2.7). Both the prevalence and reported severities of postprandial abdominal pain were lower in the T3-T9 group (prevalence of 78% and 75% of the group reporting severity between 2 (mild) and 6 (severe)), indicating that abdominal pain was generally less frequent and less severe for patients with T3-T9 pathology (Fig. 2.7; Fig. 2.11). Pain in the left lower quadrant of the abdomen was most highly reported by the T10-L2 non-scoliosis group (67%), with the severity median at 2.5 (mild) and the interquartile range extending to a severity score of 10 (very severe). The T10-L2 scoliosis and L2-L5 groups showed less reports of pain in the left lower quadrant, both showing the severity median at 0. The T3-T9 group had a severity median of 2 (mild), with the interquartile range extending to 6 (severe), indicating that the severity of LLQ pain reported by the T3-T9 group was higher than the T10-L2 scoliosis and L2-L5 groups, but lower than the T10-L2 non-scoliosis group (Fig. 2.12).

Both the prevalence and the severity of pain in the left upper quadrant of the abdomen was similar among all groups, with the prevalence of LUQ pain being slightly higher in the T3-T9 group (Fig. 2.11; Fig. 2.13). Epigastric pain described as a sensation of tightness and constipation were most highly reported by the T10-L2 scoliosis group (Fig. 2.11) but reported severity of epigastric pain was similar among the T10-L2 scoliosis, T3-T9 and L2-L5 groups (Fig. 2.14).

Constipation was most reported in the T10-L2 scoliosis group (78%), compared to other groups (63% of T3-T9 group, 56% of L2-L5 group, 50% of T10-L2 non-scoliosis group) (Fig. 2.11). Severity of constipation was also reported to be higher in the T10-L2 scoliosis group, with the severity median of the group measured at 9 (very severe), higher than the median of all other spinal groups (6 (severe) in T3-T9 group, 3 (mild) in TT10-L2 non-scoliosis group and 2 (mild) in L2-L5 group) (Fig. 2.8). The interquartile range in the T10-L2 scoliosis was highest of all groups (2.5-9 (very severe) severity), followed by the T3-T9 group (0-9 (very severe) severity).

Abdominal bloating was most highly reported by the L2-L5 group (89%), followed by the T10-L2 scoliosis (75%) and T3-T9 (72%) group (Fig. 2.11). The T10-L2 non-scoliosis group reported significantly less abdominal bloating than other groups (33%). The group with the highest severity median was the T10-L2, indicating that 50% of the T10-L2 scoliosis group reported bloating symptoms to be at least a 9 (very severe) (Fig. 2.15). This is followed by the L2-L5 group, in which 50% of the group reported bloating to be at least 6 (severe) on the severity scale. The T3-T9 group reported less severe bloating with a median of 4 (moderate) and the T10-L2 non-scoliosis group had a median of 0 (Fig. 2.15).

Nausea was most commonly reported by the T3-T9 group (100%), followed by the T10-L2 scoliosis group (87%) (Figure 2.11), with the severity of nausea also being

reported as highest in the T3-T9 group (50%) of the group reporting at least a severity of 8 (severe) and 25th-75th percentile severity between 4 (moderate) and 8 (severe) (Fig. 2.16). The T10-L2 group reported the nest highest severity, with 50% of the group reporting at least a severity of 6 (severe) and 25th-75th percentile severity between 1 (mild) and 6 (severe) (Fig. 2.16). The T10-L2 non-scoliosis group and the L2-L5 group had similar prevalence of nausea (67%) and similar severity medians at 4 (moderate).

Vomiting was most highly reported by the T3-T9 group (63%), compared to all other spinal groups (T10-L2 non-scoliosis group at 33%, L2-L5 group at 33%, T10-L2 scoliosis group at 28%) (Fig. 2.11). Reported severity of vomiting was also most reported by the T3-T9 group, with the severity median at 2 (mild) and the interquartile range from 2 (mild) to 9 (severe). The T10-L2 scoliosis, T10-L2 non-scoliosis and L2-L5 groups each had severity medians of 0 and the 75th percentile did not exceed scores of 1, 1.5, or 3, respectively (Fig. 2.5).

Abdominal gurgling was most reported in the T3-T9 group (63%), compared to the T10-L2 non-scoliosis group (33%), T10-L2 non-scoliosis group (27%) and the L2-L5 group (22%) (Fig. 2.11). The reported severity of abdominal gurgling was low among all spinal groups, however reported slightly higher in the T3-T9 group, with a median of 1 (mild) and interquartile range extending between 0 and 4 (moderate) severity (Fig. 2.17). L2-L5, T10-L2 non-scoliosis and T10-L2 scoliosis groups each had severity medians of 0 and the 75th percentiles did not exceed scores of 0, 3 and 2, respectively.

Postprandial hiccups were most often reported by the T3-T9 group (78%), compared to the T10-L2 non-scoliosis group (33%), L2-L5 group (33%) and T10-L2 scoliosis group (27%) (Fig. 2.11). The T3-T9 group also reported the highest severity of postprandial hiccups, with a median of 6 (severe), indicating that 50% of the group reports postprandial hiccups with a severity score of 6 or higher. All other spinal groups had a severity median of 0 and no group had upper whiskers not reaching higher than a score of 4 (moderate severity) (Fig. 2.4).

Regurgitation was most highly reported by the T3-T9 (67%) and T10-L2 non-scoliosis (67%) groups, compared to the T10-L2 scoliosis group (47%) and L2-L5 group (22%) (Fig. 2.11). The reported severity of regurgitation did not dramatically change among spinal groups, the T3-T9 and T10-L2 non-scoliosis group having a severity median of 1 (mild) and T10-L2 scoliosis and L2-L5 group having a severity median of 0. Most patients in spinal groups reporting regurgitation reported only mild symptom presentation, with a few outliers in the T3-T9 and T10-L2 scoliosis groups (Fig. 2.18).

Difficulty swallowing, or dysphagia, was most reported by the T3-T9 group (45%), compared to the T10-L2 scoliosis group (33%), T10-L2 group (33%) and L2-L5 group (0%) (Fig. 2.11). The T3-T9 and T10-L2 scoliosis group showed similar interquartile ranges of mild severity of dysphagia, however reported severities were overall quite mild among all spinal groups (Fig. 2.19).

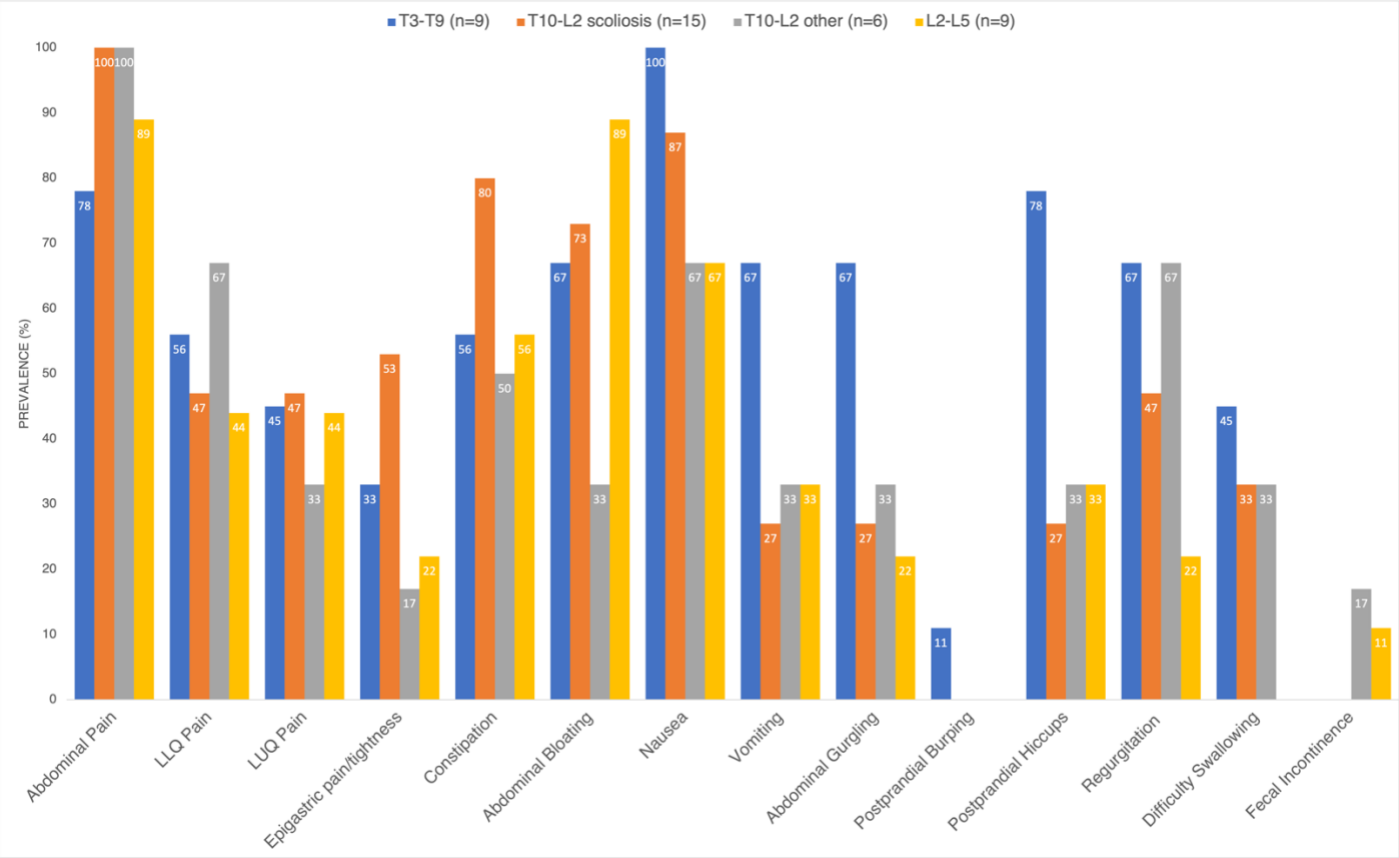

Figure 2.11 Prevalence of dominant GI symptoms reported by all patients with spinal conditions. Conditions at T3-T9 level (blue, n=9), scoliosis at T10-L2 (orange, n=15), other spinal conditions (non-scoliosis) at T10-L2 (grey, n=6), and conditions at L2-L5 (yellow, n=9). T5-T9 group and T10-L2 (non-scoliosis) group show similar dominant features. T10-L2 (scoliosis) and L2-L5 group report less pain in the left lower quadrant and more abdominal bloating. Scoliosis group reports more pain and tightness in the epigastric area of the abdomen, constipation and nausea. Values represent prevalence of symptom by percentage.

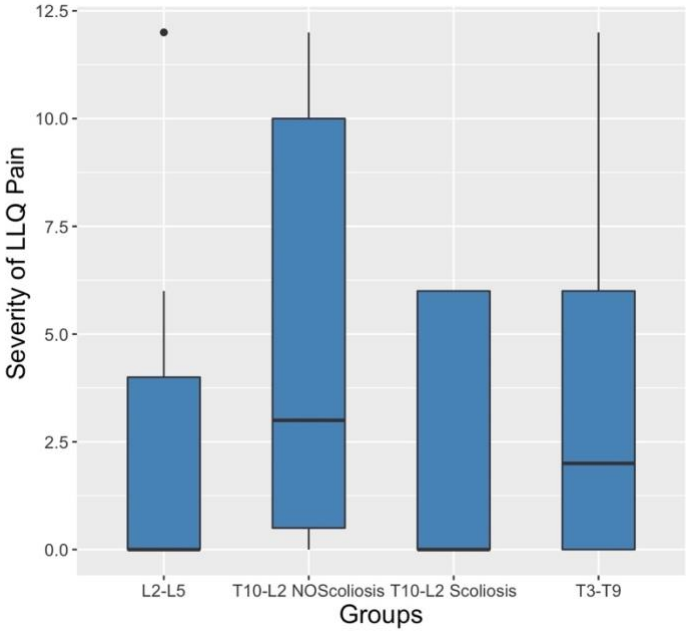

Figure 2.12 Boxplot of symptom severity scores of abdominal pain in the left lower quadrant (LLQ) of the abdomen indicating highest severity in the T10-L2 non-scoliosis group.
Boxplot outlines the distribution of LLQ pain for the four spinal condition groups: L2-L5 condition (n=4/9), T10-L2 non-scoliosis condition (n=4/6), T10-L2 scoliosis (n=7/15), and T3-T9 condition (n=5/9). The severity median was the highest in the T10-L2 non-scoliosis group at 2.5 (mild) and the interquartile range extending to a severity score of 10 (very severe). The T3-T9 group had a severity median of 2 (mild), with the interquartile range extending to 6 (severe). The reported severity of pain in the left lower quadrant in the abdomen was lower in the L2-L5 and T10-L2 scoliosis groups, with both severity medians at 0 and interquartile ranges extending to 4 (moderate) and 6 (severe), respectively.

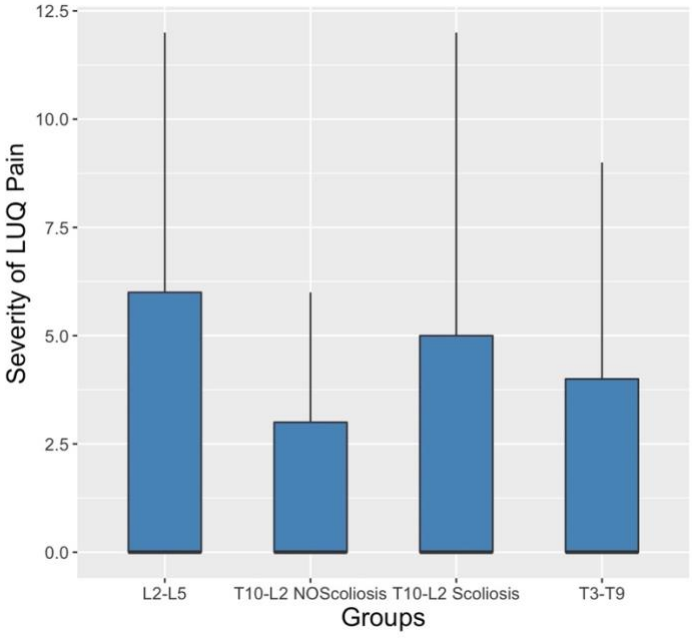

Figure 2.13 Boxplot of symptom severity scores of abdominal pain in the left upper quadrant (LUQ) of the abdomen indicating similar severity in all spinal groups.
Boxplot outlines the distribution of LUQ pain severity for the four spinal condition groups: L2-L5 condition (n=4/9), T10-L2 non-scoliosis condition (n=2/6), T10-L2 scoliosis (n=7/15), and T3-T9 condition (n=4/9). Severity scores were similar among all spinal groups, with the median of all 4 groups equal to 0.

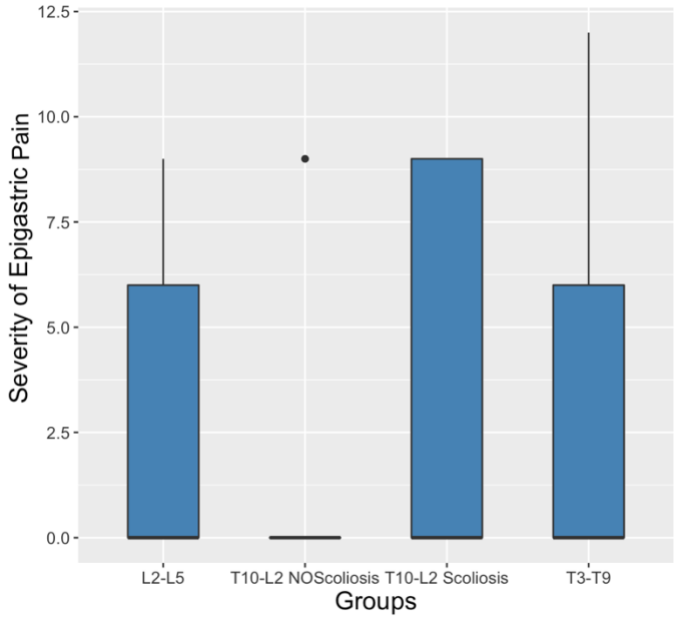

Figure 2.14 Boxplot of symptom severity scores of epigastric pain in the form of tightness indicating similar severity among all groups. Boxplot outlines the distribution of epigastric pain/tightness severity for the four spinal condition groups: L2-L5 condition (n=4/9), T10-L2 non-scoliosis condition (n=2/6), T10-L2 scoliosis (n=7/15), and T3-T9 condition (n=4/9). Severity scores were similar among all spinal groups with the median of all 4 groups equal to 0. The severity distribution was slightly higher in the T10-L2 scoliosis group, indicating that 50% of patient population was between 0 and 9 (very severe).

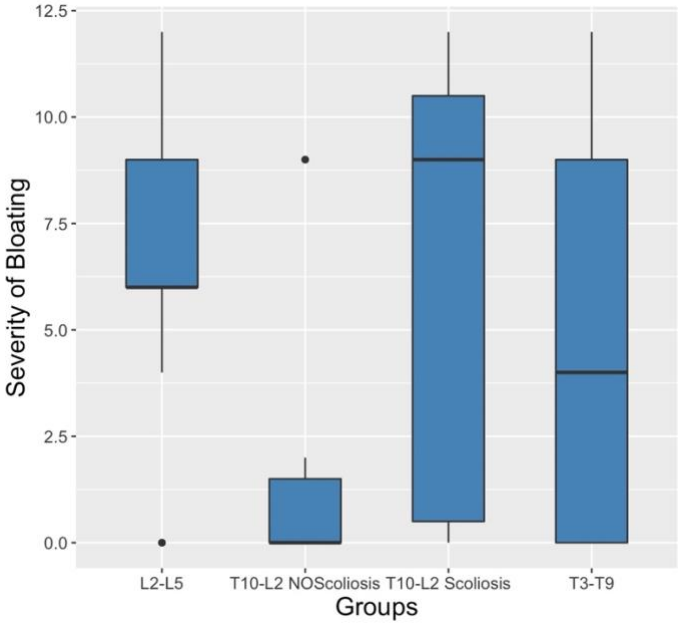

Figure 2.15 Boxplot of symptom severity scores of abdominal bloating indicating highest severity in the T10-L2 scoliosis and L2-L5 groups. Boxplot outlines the distribution of abdominal bloating severity for the four spinal condition groups: L2-L5 condition (n=8/9), T10-L2 non-scoliosis condition (n=2/6), T10-L2 scoliosis (n=11/15), and T3-T9 condition (n=6/9). Severity median was highest in the T10-L2 scoliosis group at 9 (very severe), followed by L2-L5 at 6 (severe), T3-T9 at 4 (moderate) and T10-L2 non-scoliosis at 0. The interquartile range was the smallest in the L2-L5 group, indicating that 50% of patients in the L2-L5 group reported a severity score between 6 (severe) and 9 (very severe), while 50% of patients in the T10-L2 scoliosis group reported a severity score between 0.5 (mild) and 10.5 (very severe).

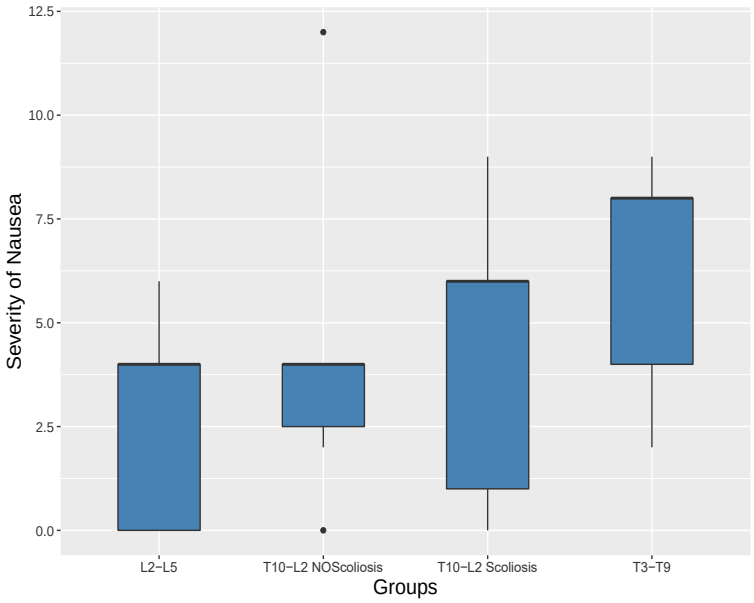

Figure 2.16 Boxplot of symptom severity scores of nausea indicating highest severity in the T3-T9 group.
Boxplot outlines the distribution of nausea severity for the four spinal condition groups: L2-L5 condition (n=6/9), T10-L2 non-scoliosis condition (n=4/6), T10-L2 scoliosis (n=13/15), and T3-T9 condition (n=9/9). The severity median was highest in the T3-T9 group at 8 (severe), indicating that 50% of the group reported a severity score of at least 8. The T3-T9 group also had the interquartile range of the highest scores. This was followed by the T10-L2 scoliosis group, which had the severity median at 6 (severe) and an interquartile range between 2 and 8 (mild and severe, respectively).

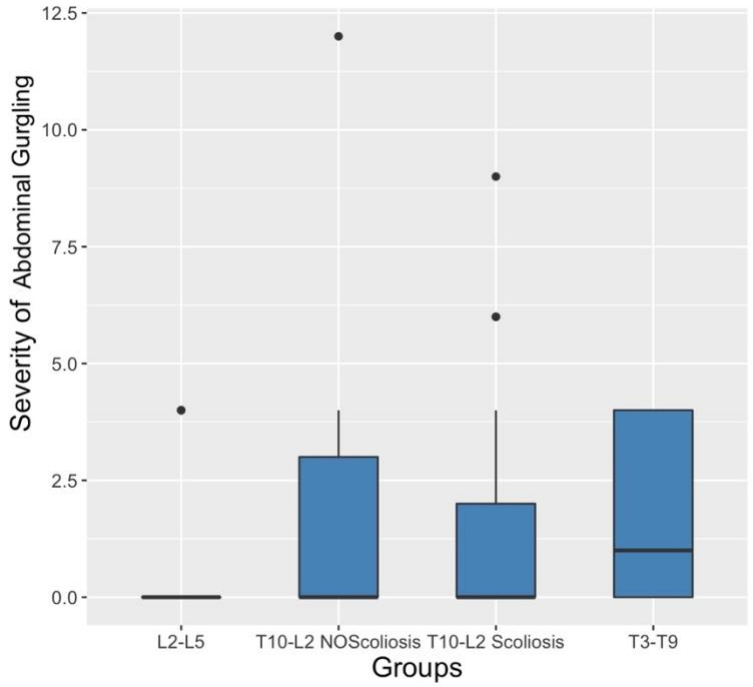

Figure 2.17 Boxplot of symptom severity scores of abdominal gurgling indicating similar severity in all spinal groups.
Boxplot outlines the distribution of regurgitation severity for the four spinal condition groups: L2-L5 condition (n=2/9), T10-L2 non-scoliosis condition (n=2/6), T10-L2 scoliosis (n=4/15), and T3-T9 condition (n=6/9). Severity median was low among all spinal groups, but highest in the T3-T9 group at 1 (mild), with the interquartile range extending between 0 and 4 (moderate). L2-L5, T10-L2 non-scoliosis and T10-L2 scoliosis groups each had severity medians of 0.

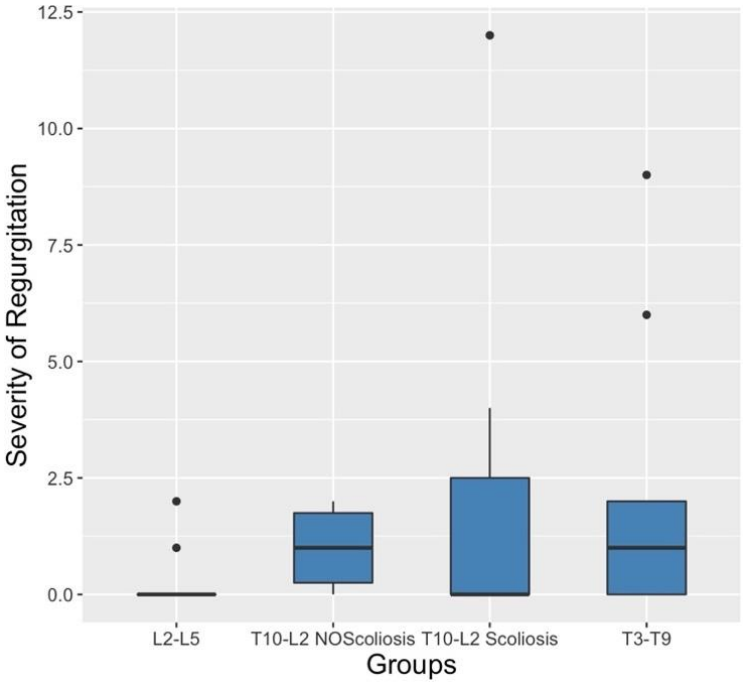

Figure 2.18 Boxplot of symptom severity scores of regurgitation indicating similar severity in all spinal groups.
Boxplot outlines the distribution of regurgitation severity for the four spinal condition groups: L2-L5 condition (n=2/9), T10-L2 non-scoliosis condition (n=4/6), T10-L2 scoliosis (n=7/15), and T3-T9 condition (n=6/9). The severity median of all spinal groups were similar, with the T3-T9 and T10-L2 non-scoliosis group having a severity median of 1 (mild) and T10-L2 scoliosis and L2-L5 group having a severity median of 0. Interquartile ranges were all between absent and mild severity.

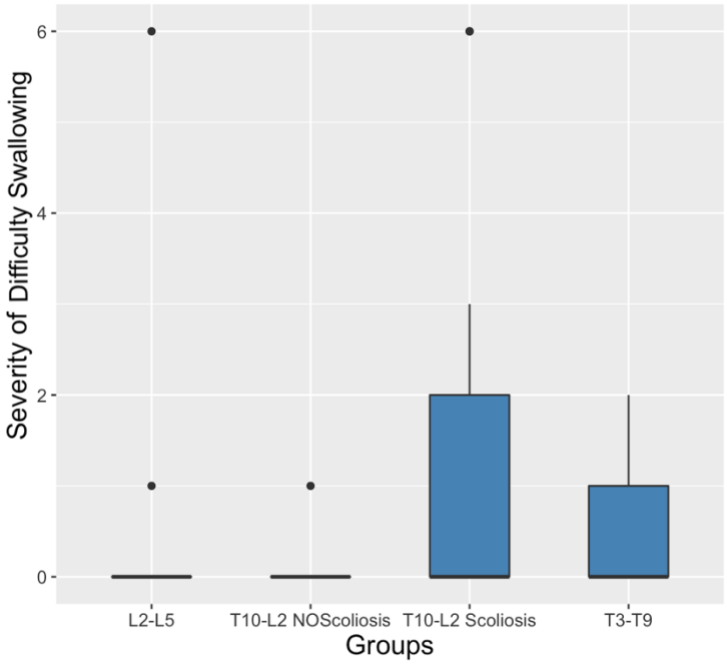

Figure 2.19 Boxplot of symptom severity scores of difficulty swallowing, or dysphagia, indicating similar severity in all spinal groups.
Boxplot outlines the distribution of regurgitation severity for the four spinal condition groups: L2-L5 condition (n=0/9), T10-L2 non-scoliosis condition (n=2/6), T10-L2 scoliosis (n=5/15), and T3-T9 condition (n=4/9). The severity median of all spinal groups is 0, with the T3-T9 and T10-L2 scoliosis group showing similar interquartile ranges of mild severity.

Postprandial hiccups, abdominal gurgling, vomiting, nausea and postprandial burping were found to be most positively correlated with the T3-T9 group (Fig. 2.20). The T3-T9 group was not correlated with postprandial abdominal pain and constipation. The T10-L2 scoliosis group was most highly correlated with postprandial abdominal pain and epigastric tightness, while negatively corelated with postprandial hiccups. The T10-L2

non-scoliosis group was found to be negatively correlated with abdominal bloating and most positively correlated with pain in the LLQ of the abdomen. The L2-L5 group was found to be most positively correlated with abdominal bloating, and not correlated with regurgitation, epigastric tightness, or nausea.

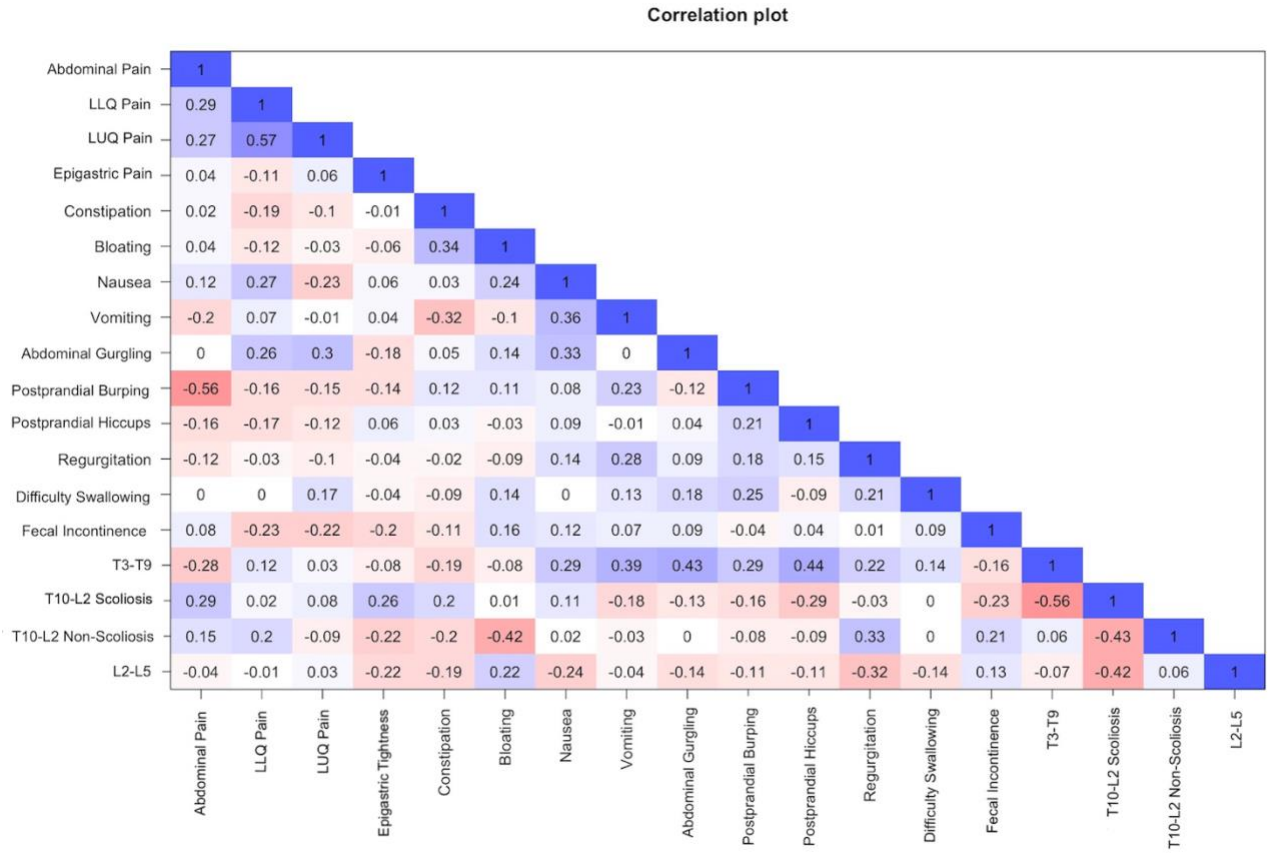

Figure 2.20 Correlation analysis plot showing correlations between symptoms and spinal groups and correlations between each symptom.

The bottom 4 rows express correlation between a symptom and a spinal group to determine symptoms indicative of a specific spinal group. A positive value indicates a positive correlation, while a negative value indicates a negative correlation. The closer to 1/-1 the stronger the correlation. We considered the strength of the evidence of a symptom as potentially indicative of spinal pathology as high (≥ 0.25), moderate (0.15-0.24) or low (≤ 0.15).

Table 2.2 Potential symptoms indicative of spinal pathology and strength of evidence

	L2-L5	***T10-L2 non-scoliosis***	***T10-L2 scoliosis***	***T3-T9***
Postprandial abdominal pain	Low	**Moderate**	**High**	Low
LLQ pain	Low	**Moderate**	Low	Low
LUQ pain	Low	Low	Low	Low
Epigastric pain/tightness	Low	Low	**Moderate**	Low
Sudden-onset constipation	Low	Low	**Moderate**	Low
Abdominal bloating	**Moderate**	Low	Low	Low
Nausea	Low	Low	**Moderate**	**High**
Vomiting	Low	Low	Low	**High**
Abdominal gurgling	Low	Low	Low	**High**
Postprandial burping	Low	Low	Low	**High**
Postprandial hiccups	Low	Low	Low	**High**
Regurgitation	Low	**High**	Low	**Moderate**
Difficulty swallowing	Low	Low	Low	**Moderate**

Based on correlation analysis of individual symptoms and spinal groups in Figure 2.20 and Table 2.2, symptoms were grouped to determine the correlation of multiple symptoms and spinal pathology groups. Symptoms were organized into seven groupings, including: vomiting > 6 hours after eating and hiccups; nausea and abdominal gurgling; nausea, vomiting and postprandial hiccups; nausea and epigastric pain/tightness; constipation and nausea; constipation, abdominal bloating and nausea; LLQ pain and nausea. Spinal pathology at T3-T9 was found to have a strong correlation with

experiencing symptoms of vomiting > 6 hours after eating and hiccups; nausea and abdominal gurgling; and nausea, vomiting and postprandial hiccups (Fig. 2.21; Table 2.3). Scoliosis pathology at T10-L2 was found to have a strong correlation with experiencing symptoms of nausea and epigastric pain/tightness; constipation and nausea; and constipation, abdominal bloating and nausea. Non-scoliosis pathology at T10-L2 was found to have a strong correlation with exhibiting both pain in the left lower quadrant and nausea.

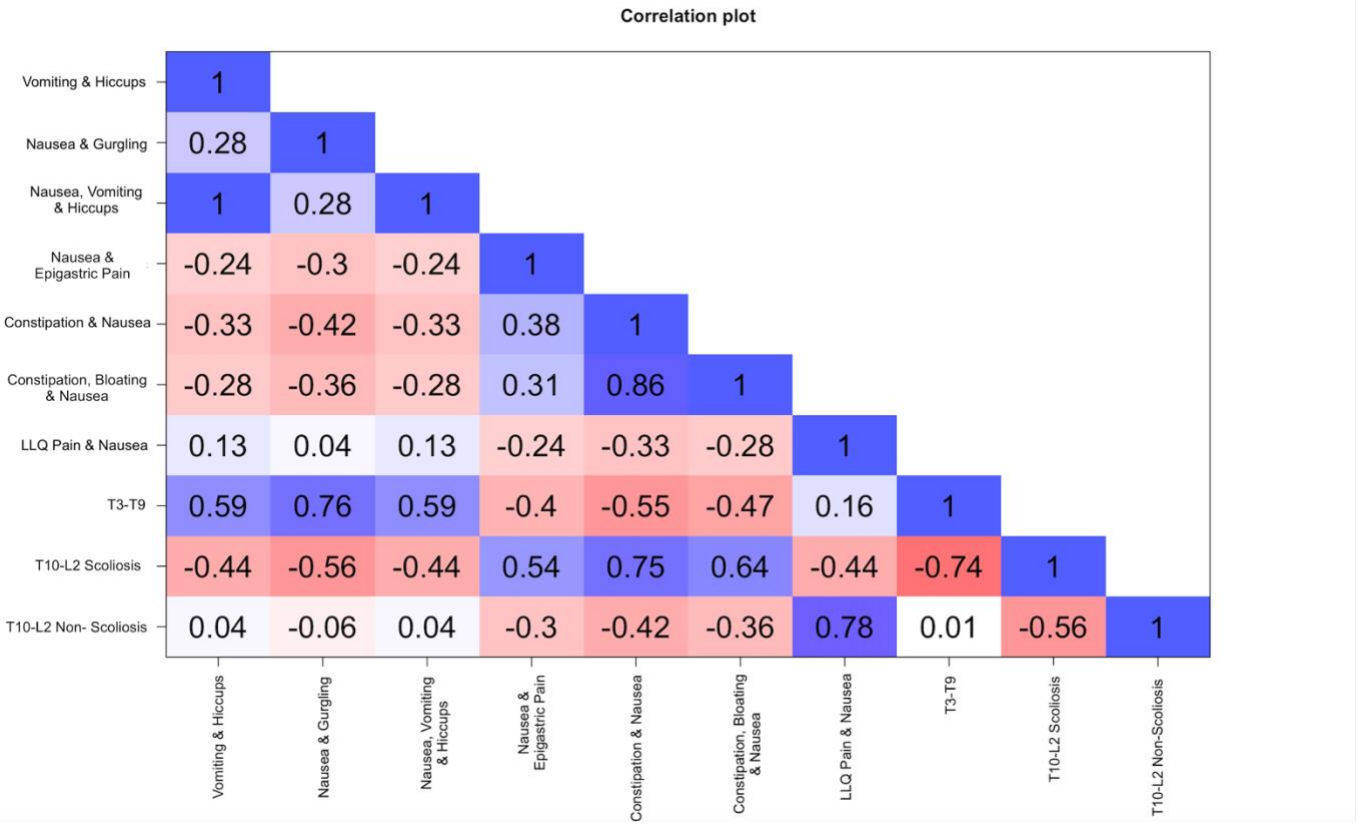

Figure 2.21 Correlation analysis plot showing correlations between multiple symptom groupings and spinal groups.
7 symptom groupings based on symptoms found in correlation analysis as shown in Figure 2.20. Symptom groupings include vomiting > 6 hours after eating and hiccups; nausea and abdominal gurgling; nausea, vomiting and postprandial hiccups; nausea and epigastric pain/tightness; constipation and nausea; constipation, abdominal bloating and nausea; LLQ pain and nausea.

Table 2.3 Main findings of potential symptoms indicative of spinal pathology

	POTENTIAL INDICATING SYMPTOMS
T3-T9	Nausea Vomiting (>6 hours after eating) Abdominal gurgling Postprandial hiccups
T10-L2 SCOLIOSIS	Epigastric pain in the form of tightness Sudden onset constipation Nausea
T10-L2 NON-SCOLIOSIS	LLQ pain Nausea with LLQ pain

2.6 Discussion

Abdominal pain in all spinal groups

Severe postprandial abdominal pain was the most dominant symptom reported in all patients with spinal pathology, regardless of pathological spinal region. Throughout all spinal groups, postprandial abdominal pain was most highly reported in the left quadrants of the abdomen. The mechanism of abdominal pain involves afferent fibres running through the DRG of the thoracolumbar spine. Afferent fibres run parallel to the thoracolumbar efferent pathways, involving innervation of the esophagus, stomach and duodenum arising from T5-T9 vertebrae and innervation of the jejunum, ileum and colon arising from T10-L2 (Browning & Travagli, 2014). Patients reporting severe postprandial abdominal pain without functional or systemic pathology is indicative of potential spinal pathology within the thoracolumbar region.

Pain in the left lower quadrant of the abdomen was most reported by patients in the T10-L2 non-scoliosis group. Findings show T10-L2 non-scoliosis pathology to be significantly correlated with symptom presentation of nausea and LLQ pain, suggesting that this group of symptoms presented together may be indicative of T10-L2 non-scoliosis pathology. Localized pain in the left lower quadrant often involves the colon, particularly the descending and sigmoid colon, due to anatomical position of the organ (Hammond, Nikolaidis, & Miller, 2010). The lumbar splanchnic and hypogastric nerves are responsible for the innervation of the distal colon and arise from T12-L3 of the thoracolumbar spinal cord, with afferent fibres running parallel to efferent fibres. Afferent fibres run through the DRG of the thoracolumbar spine, transmitting afferent impulses to the CNS. Spinal condition or injury at the T10-L2 level may result in the dysregulation of afferent signals being sent to brain centers, causing the interpretation of pain without systemic cause. Pain may increase postprandially due to distention from food entering the GI tract stimulating afferent sensory neurons, triggering signals to be sent to the CNS. The mechanisms of scoliosis pathology and why left lower quadrant pain is not seen as commonly in the T10-L2 scoliosis group needs to be further investigated.

Nausea in all spinal groups

Nausea has been found to be associated with increased activation of the sympathetic nervous system and decreased activation of the parasympathetic nervous system (Cowings, Suter, Toscano, Kamiya, & Naifeh, 1986) (Singh, Yoon, & Kuo, 2016). Abnormal decreases in fundic tone and LES pressure, indicating a decrease in vagal activity and increase in sympathetic activity, have been found to result in the activation of gastric afferents, inducing nausea (Schaub et al., 2014) (Hornby, 2001). Sympathetic innervation of the esophagus and stomach, playing a role in the LES pressure and fundic tone, arises from T5-T9 of the thoracolumbar spinal cord.

Here we report that nausea is most prevalent and reported as most severe in patients with spinal conditions located at T3-T9, followed by patients with scoliosis from T10-L2, hence we can infer that spinal pathology within these regions of the spinal cord can cause severe nausea. The L2-L5 group reported low prevalence of nausea, indicative of the symptom being associated with thoracic and thoracolumbar pathology. Due to nausea not being as prevalent or severely reported in the T10-L2 non-scoliosis group compared to the scoliosis group within the same spinal region, in addition to the neuroanatomy of esophageal and gastric sympathetic innervation, it is hypothesized that neuropathy of spinal nerves particularly in the T5-10 region may induce an excitatory effect on esophageal and gastric sympathetic innervation, resulting in symptoms of nausea. It is possible that the heightened exhibition of nausea by the T10-L2 scoliosis group may be due to compensatory effects in the T5-T10 region due to scoliosis in the T10-L2 region rather than neuropathy within the T10-L2 region itself, however this needs to be further investigated.

Gastroparesis, characterized by delayed gastric emptying due to gastric motor dysfunction, can cause main symptoms of nausea, vomiting and abdominal bloating (Camilleri et al., 2018). 2/9 patients in the T3-T9 group, 2/15 patients in the T10-L2 scoliosis group, 2/6 patients in the T10-L2 non-scoliosis group and 4/9 patients in the L2-L5 group have a diagnosis of gastroparesis through confirmed testing of delayed gastric emptying, however 67% of spinal patients did not undergo delayed gastric emptying studies due to lack of requirement based on clinical impression (Table 2.1). While gastroparesis is likely a contributing factor to spinal patients with nausea, vomiting, and other symptoms of gastroparesis, it is not prevalent in most spinal patients in this study, indicating other underlying pathology for their symptoms. The pathophysiology of gastroparesis has substantial gaps in knowledge, so it is important to also consider the possibility of spinal pathology-induced extrinsic neuropathy causing gastric dysmotility related to delayed gastric emptying.

Bloating in all spinal groups

Abdominal bloating has been suggested to be due to uncoordinated intestinal motility (Azpiroz & Malagelada, 2005), such as lack of SPWs. SPWs often start in the proximal colon or occur following the end of an HAPW and are the motor pattern most closely

associated with gas expulsion. It is therefore our hypothesis that impairments in SPWs restricts the ability of gas-expulsion, resulting in gas retention and symptoms of bloating. SPWs are initiated by parasympathetic activity via the vagus nerve in the proximal colon. In addition to the SPWs, the coloanal reflex needs to be generated to open the anal sphincters for expulsion. The coloanal reflex involves the relaxation of the internal and external anal sphincter that occurs autonomically in response to the generation of an HAPW or SPW in healthy subjects. Increases in sympathetic activity of the proximal and distal colon may result in the inhibition of SPW generation that is mediated by the vagus, hence causing bloating. The sympathetic innervation of the colon arises from T10-L3 of the thoracolumbar spinal cord (Yoham & Bordoni, 2022).

Abdominal bloating was most reported in the L2-L5 spinal group, but also prevalent among the T10-L2 scoliosis and T3-T5 group. While most prevalent in the L2-L5 group, severity of bloating was highest in the T10-L2 scoliosis group, which may be due to the dysregulation of the sympathetic innervation of the colon arising from the T10-L2 level. The T10-L2 non-scoliosis group reported less prevalence and lower severity of abdominal bloating compared to all other spinal groups. Investigations into scoliosis pathology versus non-scoliosis-spinal pathology of the same spinal regions need to be further investigated. One immediate objective for our group will be to test autonomic functioning in these patients using the Baevsky index for sympathetic functioning, both under relaxed conditions and in response to stimuli such as active standing and stomach filling.

Symptoms associated with spinal conditions of T3-T9

The T3-T9 spinal group reported the highest prevalence and the most severe presentation of vomiting > 6 hours after a meal, postprandial hiccups, and abdominal gurgling. Findings show T3-T9 pathology to be significantly correlated with symptom presentation of nausea, vomiting > 6 hours after a meal, postprandial hiccups, and abdominal gurgling, suggesting that this group of symptoms presented together may be indicative of T3-T9 spinal pathology.

Vomiting has been found to be associated with intrinsic retrograde contractions of the duodenum and stomach, with the relaxation of the LES and with increased sympathetic tone (Lang et al., 1993). Increased sympathetic tone may inhibit essential parasympathetic innervation for normal motility. When vomiting centres in the brain are activated, through triggers such as distention from upper GI organs sending afferent impulses to the brain, motor pathways descend from the vomiting center and efferent pathways travel within vagal and sympathetic nerves to the GI tract (Becker, 2010). Clinical presentation of vomiting in spinal patients can be worsened postprandially, however occurs also in the absence of eating, indicating that the vomiting mechanism is not only triggered by distention, but there must be underlying pathology causing vomiting in the absence of food intake. Sympathetic innervation of upper GI organs arises from

T5-T9 of the thoracolumbar spinal cord, hence, disruption of innervation pathways due to spinal conditions or injury within this spinal region may result in dysregulation of either afferent or efferent pathways involved in the mechanism of vomiting. Disruption to afferent pathways may cause the transmission of afferent impulses to the vomiting center even without distention, or disruption to efferent pathways may cause relaxation of the LES and increased sympathetic tone, inducing vomiting. This would provide an explanation as to why patients in the spinal group report vomiting even without the initial triggering of food intake-induced distention.

Hiccups have been described as spontaneous myoclonic contractions of the diaphragm (Steger, Schneemann, & Fox, 2015), in which the mechanism is due to irritation of the reflex arc (Rouse & Wodziak, 2018). The reflex arc involves afferent neurons from phrenic, vagus and sympathetic nerves (T5-T12), sending afferent signals to the areas and brain centers of the CNS involved in hiccups. Hiccup brain centers then involve efferent pathways of the phrenic nerve to the diaphragm and an accessory nerve to the intercostal muscles (Rouse & Wodziak, 2018). The hiccup mechanism is triggered by irritants or disruptions to afferent, central, or efferent pathways involved in the reflex arc, including distention of the stomach, over-excitement, or anxiety. Greene et al. performed high-resolution esophageal manometry on a male patient with severe cyclical hiccups, finding that while hiccupping, the patient had a mechanically defective lower esophageal sphincter (LES) and absence of esophageal peristalsis, which improved when the patient was not actively hiccupping (Greene, Oh, Worrell, & Hagen, 2016). This suggests that hiccupping is associated with incompetence of the LES and inhibition of esophageal peristalsis, both associated with increased sympathetic tone (Diamant, 1989). In the present study, postprandial hiccups are most reported in patients with spinal conditions located at the T3-T9 region of the spinal cord, and also reported as most severe by this spinal group. Sympathetic efferents arising from T5-T9 are responsible for esophageal and gastric sympathetic innervation, hence, spinal conditions within this region may cause overexcitation of these sympathetic pathways, resulting in dysregulation of the reflex arc and the triggering of hiccups. Afferent pathways involved in the reflex arc, such as those detecting excessive gastric distention which trigger the reflex arc, also pass through the thoracolumbar spinal region from T5-T12. Spinal conditions causing disruptions to these afferent pathways involved in the reflex arc may also cause disruption of signals being transmitted to the hiccup centers of the CNS, hence inducing hiccups even when triggers may not be present.

Abdominal gurgling was also mostly reported in the T3-T9 group. Abdominal gurgling is a gas-related symptom of the upper GI organs (Waller et al., 2011), involving the movement of gas and liquids in the GI tract. Gas ventilation from the stomach occurs with relaxation of the upper esophageal sphincter (UES), which has been found to be positively associated with TLESRs (Kahrilas, 2022). TLESRs have been shown to indicate a decrease in vagal activity and increase in sympathetic activity (Schaub et al.,

2014). Therefore, it is possible that increased activity of the sympathetic innervation of the esophagus and stomach (arising from T5-T9 of the spinal cord) due to spinal pathology may cause increased TLSERs, hence decreasing the occurrences of gas ventilation and increasing the occurrence of upper abdominal gurgling.

Regurgitation of food has been described as retrograde migration of gastric contents, up the esophagus into the mouth (Antunes, Aleem, & Curtis, 2017). Regurgitation has been found to also be associated with low LES pressure and TLESRs (Richter & Rubenstein, 2018), correlating with an increase in sympathetic tone (Schaub et al., 2014). In the mechanism of TLSERs, gastric distention triggers afferent neurons in the stomach, projecting the signal through afferent fibres, through the thoracolumbar spinal cord and to the DMV, which contains vagal efferent cell bodies, ultimately mediating LES pressure and TLSERs (Mittal et al., 1995). Regurgitation was most reported by patient with spinal conditions at the T3-T9 level and non-scoliosis at T10-L2. Disruption of afferent pathways at the thoracolumbar level may result in the disruption of the transmission of signals responsible for triggering parasympathetic pathways to mediate LES pressure or TLSERs, resulting in symptoms of regurgitation. As LES and TSLERs are also involved in nausea, vomiting and hiccupping, it is possible for this mechanism to involved in the pathophysiology of each of those symptoms in spinal patients as well. Alternately, disruption of sympathetic efferent pathways at the T3-T9 level due to spinal conditions may cause increases in sympathetic tone, hence resulting in regurgitation of food.

Symptoms associated with scoliosis of T10-L2

The T10-L2 scoliosis spinal group reported highest prevalence of epigastric pain/tightness, and the most prevalent and severe presentation of chronic, sudden-onset constipation. Findings show T10-L2 scoliosis pathology to be significantly correlated with symptom presentation of nausea, epigastric pain in the form of tightness, and abdominal bloating, suggesting that this group of symptoms presented together may be indicative of T10-L2 scoliosis pathology.

Pain in the epigastric region, often experienced as tightness, can be caused by organs derived by the embryonic foregut; the esophagus, stomach, and proximal duodenum (Macaluso & McNamara, 2012). Nociceptors within these organs transmit nociceptive signals via visceral afferent receptors to the thoracolumbar DRG (T5-T9), which are then projected to brain centres for interpretation (Robinson & Perkins, 2016). Spinal conditions, such as stenosis, may cause neurological disruption of spinal pathways involved in the innervation of the gut. There are two potential mechanisms of dysregulation or dysfunction of spinal pathways involved in the presence of epigastric pain or tightness, or a combination of the two. One potential mechanism is the dysregulation of T5-T9 thoracolumbar efferent pathways involved in the sympathetic innervation of the esophagus, stomach, and proximal duodenum. If spinal pathology results in overactivation of T5-T9 sympathetic pathways and esophageal or gastric

motility is inhibited, excess distention may occur after food intake due to lack of fundic relaxation. Nociceptors within upper GI organs can transmit signals from excess distention to the thoracolumbar spinal cord, to brain centres, resulting in the perception of pain in the epigastric region. Another potential mechanism is the dysregulation of the visceral afferent pathways running through the thoracolumbar DRG due to disruption from a spinal condition. Disruption at the thoracolumbar level of the afferent signals travelling from the esophagus, stomach, and/or proximal duodenum (T5-T9) may affect the transmission of sensory pain signals from the upper GI organs, resulting in the interpretation of pain in the epigastric region without systemic pathology. This may also provide reasoning as to why patients do not have positive findings in GI diagnostic investigations. In this study, the T10-L2 scoliosis group reported more prevalence of epigastric pain than the T3-T9 group. T10-L2 is responsible for the sympathetic innervation of the jejunum, ileum, proximal and distal colon, and the rectum, in which visceral pain is typically localized to the periumbilical region (Macaluso & McNamara, 2012). This study however found T10-L2 scoliosis to show significant accounts of epigastric pain in the form of tightness, which was not seen in the T10-L2 non-scoliosis group. A possible explanation for this is the compensatory mechanisms seen in people with scoliosis for the regulation of body posture and balanced weight distribution (Czupryna, Nowotny-Czupryna, & Nowotny, 2012). Compensatory mechanisms often include muscles in the back permanently contracting on the concave side of the spinal curve to maintain spinal alignment, or secondary (compensatory) curves in the spine. The hypothesis of compensatory mechanisms effecting other regions of the spine should be taken into consideration when looking at scoliosis, such as the possibility of back muscle contraction and/or secondary spinal curves applying pressure to secondary regions of the spine. Compensation for T10-L2 scoliosis in other regions of the spine, such as the upper thoracolumbar (T5-T9) region, may cause neuropathy or dysregulation of spinal nerves causing secondary symptoms linked to upper GI organs, however the pathophysiology behind scoliosis and upper GI organ dysmotility needs to be further investigated.

The defecation process involves the defecation reflex, which if dysregulated or dysfunctional can cause chronic constipation. The defecation reflex involves the activation of afferent neurons, projecting to Barrington's nucleus and ultimately initiating high amplitude pressure waves in the proximal colon via parasympathetic pathways, dominantly via nerves from the vagal motor nucleus exciting vagal efferent neurons in the proximal colon (Valentino et al., 1999). Sympathetic innervation arising from T10-T11 is responsible for the innervation of the proximal colon via the lumbar splanchnic nerve, while sympathetic innervation arising from T12-L2 is responsible for the innervation of the distal colon and rectum via the lumbar splanchnic nerve and hypogastric nerve (Harrington, Castro, Erickson, Grundy, & Brierley, 2018). The spinal curve involved in scoliosis at the thoracolumbar level may cause dysregulation of the sympathetic pathways, hence increasing sympathetic tone and inhibiting the propulsive motor patterns

required for defecation. High prevalence and high severity scores of constipation seen in patients in this study with scoliosis at this spinal level suggests T10-L2 spinal pathology inducing sudden-onset constipation.

Questionnaire

The questionnaire developed to collect patient symptom and quality of life information has proven useful as a resource for clinical practice. The diagnosis process for patients with complex GI dysmotility, beyond traditional GI investigations such as abdominal CT scans, gastric emptying study (GES), etc., consists mainly of clinical judgement and corresponding suggestions of dietary and lifestyle modifications. For patients with mostly negative findings in GI investigations and no clear pathological diagnosis, this can lead to little to no answers and limited treatment options. This questionnaire was developed to provide a complete, systemic assessment of both pathological and neurological symptoms that may be directly or indirectly involved in their GI condition. It was designed in great detail, intentionally outlining a large number of symptoms that may often be overlooked or not mentioned in traditional clinical assessment. This has allowed us to identify symptoms such as postprandial hiccups, which we have not often seen as commonly discussed in clinical assessments by clinicians, as symptoms indicative of spinal pathology at the T3-T9 level. Prior to the questionnaire assessments in our study, few patients (n=3) had postprandial hiccups in their clinical assessment notes, however after completion of questionnaire assessments, (n=16) patients reported significant presence of the symptom, otherwise unmentioned in the clinical assessments from general practitioners and GI specialists. The use of the questionnaire can be most useful for patients with unremarkable GI investigations and unclear diagnosis and/or pathology. The use of the questionnaire, taking into consideration symptom findings of this study, may help in determining the pathophysiology behind their condition, in particular, potential spinal conditions causing neuropathy of autonomic spinal nerves, to look into as the primary pathology of their symptoms. Determining the pathology behind their condition allows for the opening of treatment options for their condition, with treatments targeting the primary cause of their condition.

The initial design of the questionnaire aimed to outline a large variety of symptoms in order to provide a complete assessment of patient condition as well as any symptoms that may be indicative of spinal pathology. Compared to clinical assessment, the questionnaire assessment is highly extensive and outlines many symptoms not frequently brought up in traditional clinical assessments. This was incorporated into the questionnaire design intentionally, with the aim of eventually condensing questionnaires based on findings of symptoms most clinically relevant in complex GI patients. The shoulder and neck subgroup can be condensed or removed, as questions of nodules

and/or tenderness within these regions were not found to be significantly relevant in the investigation of GI and neurological symptoms. It is more beneficial gaining information about pain radiating from their abdomen to other regions of the body, which is outlined in the abdominal symptom subgroup and is more indicative of neurological pathology. In the mouth/throat subgroup, questions including throat bleeding, blood in vomitus, and discoloured (black or brown) vomitus could be removed due to minimal to no spinal patients reporting these symptoms. The completion of the questionnaire was found to be most consistent and efficient when completed with the clinician or researcher compared to having the patient fill out the form on their own, which can be implemented in future studies. This helped eliminate challenges associated with self-report assessment such as misinterpretation of questions, incorrectly inputted responses (skipping questions). Through discussion with patients, clinicians are able to determine a more accurate scoring of their symptoms based on the scoring scale, accounting for some response bias and extreme response bias as a result of completing self-assessments at home. When completing the assessment with patients, either in-person, virtually or via phone call, we often found differences in patient responses compared to the self-reported assessments completed on their own. Differences most often involved higher scores with discussion versus their questionnaire response. For example, it was common for patients to report their symptoms to a clinician as an 8/10 on the pain severity scale, however, would indicate the severity to be 'moderate', equal to a 4-6/10 on the pain severity scale, in the at-home self-report questionnaire. Symptoms exhibited by patients are complex, and after discussion with patients, many reported difficulties in giving one ranking or score for symptoms due to fluctuation of their condition. This leads us to believe that the questionnaire is best utilized by the clinician as an addition to their traditional clinical assessment. Moving forward with the questionnaire, it would be possible to condense the questionnaire to become more clinically useful and efficient by taking into consideration the findings through this study. In-depth questioning of muscle soreness, particularly in the shoulder and neck symptom subgroups can be condensed due to limited findings with clinical relevance.

Summary of findings

This study has allowed for the identification of clinical features of complex GI dysmotility, as well as the initial steps in determining symptoms of GI dysmotility that are indicative of thoracic and lumbar spinal pathology. The diagnosis process for patients with complex GI dysmotility, non-specific symptoms and negative GI investigation findings has led to limited diagnoses nor successful treatment options, causing a deteriorating quality of life. Broadening the diagnosis process to incorporate the investigation of neurological pathology is crucial for patients suffering with complex dysmotility. The identification of

primary pathology of dysmotility will allow for the advancement of future treatment options targeting the primary cause of symptoms.

The questionnaire was able to identify symptoms associated with pathological spinal location and thoracolumbar scoliosis, as outlined in Table 2.2 and Table 2.3. The questionnaire questions targeting these particular symptoms are able to suggest spinal pathology based on symptoms exhibited. While patients are extremely heterogeneous and multiple factors, such as anxiety and stress levels, can play large roles in the presentation of their condition, the symptoms determined in this study can be included as the fundamental symptoms used in the continued study of GI dysmotility with spinal pathology. In particular, we suggest further study of epigastric pain in the form of tightness as a symptom indicative of spinal pathology of scoliosis at the T10-L2 level and postprandial hiccups, abdominal gurgling and vomiting > 6 hours after food consumption as symptoms indicative of spinal pathology at the T3-T9 level. Future studies confirming these as indicative symptoms for spinal pathology would allow for the shifting of treatments away from symptom management and towards the introduction of treatments targeting specific pathology of patient condition, such as neuromodulation therapies.

The original objective was to include autonomic function analysis through heart rate variability (HRV) assessments. Autonomic function analysis would provide information on patient autonomic activity and reactivity, hence would help to infer whether spinal conditions are inducing autonomic dysfunction-related GI symptoms. The COVID-19 pandemic did not allow for in-person patient visits, therefore making it not possible to obtain HRV data from patients to assess autonomic function. Assessment of autonomic function should be utilized in the future study of complex GI dysmotility with spinal pathology.

Limitations

This study has several limitations, including the small subject population size. Due to the largely heterogeneous nature of subjects with complex GI dysmotility, it is important to have a large sample size to best represent the spinal location condition. Having a larger *n* value in future studies will also allow for further categorization of spinal condition in addition to spinal location, as we have done in this study with scoliosis. We found several differences between scoliosis and non-scoliosis conditions within the same spinal location; therefore, differences of additional spinal conditions will be of great value in future studies. Another limitation of this study is the use of a self-report questionnaire, which can result in response bias causing inaccuracy in some of the reported data, particularly when looking at severity scores. Based on the challenges with at-home, self-report assessments, we would suggest for future studies to incorporate the questionnaire

into clinical assessments with the health care professional in attempts to help eliminate some of the misunderstanding of symptoms and gain the most accurate severity scoring.

Conclusions

In conclusion, this study has successfully identified the clinical features and symptoms of complex GI dysmotility via questionnaire. It has also identified multiple symptom groupings that can be used as symptom markers for the future of the diagnosis and development of treatment options for complex GI dysmotility with thoracic and lumbar spinal pathology.

Supplementary

Supplementary Table 1. All patients' spinal pathology and symptom severity score data.

	Spinal Condition	Spinal Group	Condition Location	Abdominal Pain	LLQ Pain	LUQ Pain	Epigastric Pain	Constipation	Bloating	Nausea	Vomiting	Abdominal Gurling	Postprandial Burping	Postprandial Hiccups	Regurgitation	Difficulty Swallowing	Fecal Incontinence
PATIENT #1	Disc bulging	T3-T9	T3	6	4	4	0	9	4	6	2	1	0	1	1	1	0
PATIENT #2	Disc misalignment	T3-T9	T5	6	0	0	9	6	9	8	0	4	0	9	0	0	0
PATIENT #3	Stenosis	T3-T9	T5-T7	6	6	6	6	9	4	9	4	4	0	1	0	1	0
PATIENT #4	Scoliosis	T3-T9	T5-T7	9	8	9	1	0	12	9	9	1	0	0	0	1	0
PATIENT #5	Stenosis	T3-T9	T5-T9	12	12	4	0	0	0	4	2	4	0	0	2	0	0
PATIENT #6	Degenerative	T3-T9	T6	2	0	0	12	0	0	2	9	0	0	12	6	0	0
PATIENT #7	Kyphosis	T3-T9	T8	0	0	0	0	8	2	8	0	0	1	6	0	2	0
PATIENT #8	Scoliosis & Osteophytes	T3-T9	T8-T10	6	0	0	0	9	9	8	0	4	0	6	9	0	0
PATIENT #9	Scheuermann's	T3-T9	T9	2	2	0	0	0	0	2	8	0	0	9	2	0	0
PATIENT #10	Scoliosis	T10-L2	T7-T10	9	0	0	0	6	0	9	6	0	0	0	0	0	0
PATIENT #11	Scoliosis	T10-L2	T10	8	10	4	0	10	10	1	0	9	0	0	1	0	0
PATIENT #12	Scoliosis	T10-L2	T10-L2	9	0	0	9	9	9	6	0	0	0	6	4	0	0
PATIENT #13	Scoliosis	T10-L2	T10-L2	6	0	0	4	12	9	8	2	0	0	0	1	0	0
PATIENT #14	Scoliosis	T10-L2	T10-L2	6	6	8	10	0	12	1	1	0	0	0	1	2	0
PATIENT #15	Scoliosis	T10-L2	T10-T12	9	0	0	9	9	12	6	0	0	0	2	4	0	0
PATIENT #16	Scoliosis	T10-L2	T10-T12	9	6	2	0	9	12	4	0	4	0	9	0	0	0
PATIENT #17	Scoliosis	T10-L2	T11-L1	6	6	6	0	0	0	0	0	0	0	0	12	2	0
PATIENT #18	Scoliosis	T10-L2	T11-L3	9	0	0	0	9	9	6	0	6	0	0	0	6	0
PATIENT #19	Scoliosis	T10-L2	T12	9	6	2	0	9	4	1	0	6	0	0	0	0	0
PATIENT #20	Scoliosis	T10-L2	T12-L1	9	6	0	9	9	0	4	0	0	0	9	0	0	0
PATIENT #21	Scoliosis	T10-L2	T12-L1	9	0	0	0	9	4	9	12	0	0	0	4	3	0
PATIENT #22	Scoliosis	T10-L2	T12-L1	12	6	12	0	4	12	6	0	0	0	0	0	0	0
PATIENT #23	Scoliosis	T10-L2	T12-L2	12	0	12	9	9	0	0	0	0	0	0	0	0	0
PATIENT #24	Scoliosis	T10-L2	T12-L3	9	0	0	9	0	9	6	0	0	0	0	0	6	0
PATIENT #25	Disc herniation	T10-L2	T9-T11	9	0	6	9	6	0	0	0	0	0	4	1	1	0
PATIENT #26	Kyphosis	T10-L2	T10-L2	2	2	0	0	0	0	2	8	0	0	9	2	0	0
PATIENT #27	Kyphosis	T10-L2	T10-L2	4	0	0	0	6	2	4	0	12	0	0	1	0	6
PATIENT #28	Tarlov cyst	T10-L2	T10-T11	12	12	0	0	0	0	12	0	0	0	0	0	0	6
PATIENT #29	Vertebral hemangiomas	T10-L2	T11	4	4	0	0	6	9	4	0	0	0	0	2	0	0
PATIENT #30	Degenerative	T10-L2	T12-L1	12	12	4	0	0	0	4	2	4	0	0	0	0	0
PATIENT #31	Stenosis	L2-L5	L2-L3	6	6	6	6	9	4	0	4	4	0	1	0	1	0
PATIENT #32	Soft tissue edema	L2-L5	L2-L5	12	0	12	0	0	6	0	0	0	0	6	0	0	0
PATIENT #33	Degenerative	L2-L5	L3-L5	9	0	0	9	0	9	6	0	0	0	0	0	6	0
PATIENT #34	Degenerative	L2-L5	L4-L5	12	1	8	8	2	6	4	3	0	0	0	0	0	2
PATIENT #35	Degenerative	L2-L5	L4-L5	12	0	0	0	6	12	0	0	0	0	0	0	0	0
PATIENT #36	Stenosis	L2-L5	L4-L5	6	0	0	0	9	9	0	0	0	0	0	0	0	0
PATIENT #37	Disc bulging	L2-L5	L4-L5	4	4	0	0	6	9	4	0	0	0	0	2	0	0
PATIENT #38	Disc bulging	L2-L5	L4-L5	12	12	4	0	0	0	4	2	4	0	0	0	0	0
PATIENT #39	Disc herniation	L2-L5	L4-L5	6	0	0	0	0	6	4	4	0	0	0	1	0	9

3 Home TENS for GI dysmotility & questionnaires

3.1 Introduction

Our initial objective was to perform low level laser therapy (LLLT) as our first line of treatment for patients with complex GI dysmotility, and although HiREB approval was obtained, the treatment could not proceed because COVID-19 rules at the hospital did not allow outpatients to come in for experimental treatment. As a consequence, we designed a study for which we obtained HiREB approval that involved home treatment by TENS, a home bioelectric neuromodulation treatment for patients with complex GI dysmotility involving upper GI symptoms such as nausea. TENS treatment allows for the stimulation of extrinsic autonomic neural pathways without the invasiveness neuromodulation with implanted electrodes (Payne et al., 2019). The non-invasive and portable nature of the treatment allows for at-home use and for the potential of accessible long-term treatment (Palmer, Martin, Steedman, & Ravey, 1999). There may be more benefits to home treatment such as elimination of travel time and costs. It also allows for the treatment of patients that may have geographical or travel limitations. Virtual training adheres to restrictions due to the COVID-19 pandemic or new upcoming pandemics, allowing for full treatment of patients regardless of pandemic restrictions. There is limited research on the effect of thoracic spinal TENS neuromodulation, however, we hypothesized that stimulation of thoracolumbar spinal afferents and efferents responsible for innervating the upper GI tract can successfully treat dysmotility symptoms.

Objective:

- To assess the feasibility and potential problems with at home, self-directed treatment
- To assess the effect of neuromodulation of the thoracolumbar spine on symptoms of complex GI dysmotility with thoracolumbar spinal pathology
- To assess the efficacy of the self-report questionnaire in monitoring GI symptom in response to TENS treatment

3.2 Methods

Patient Population

The focus was on patients with complex gastrointestinal dysmotility with left colon dysmotility but also with significant symptoms in upper GI.

We gave five males and thirty-six females aged 18-77 years the option of doing TENS at home, by explaining the procedures and giving them a one-time virtual training

in using the TENS so that they could make an informed decision (see Table 3.1 for demographic information). All patients given the option of TENS treatment showed severe GI dysmotility with poor response to pharmacological treatments. Patients had functional bowel dysfunction as defined by specific Rome IV criteria and had spinal pathology as shown by diagnostic spinal imaging such as X-ray, MRI or CT scans, including scoliosis, degenerative changes, herniated disc, non-specific back pain, post trauma (e.g., motor vehicle accidents (MVAs)) and spinal stenosis. Upper GI dysfunction seen in the patients as defined by Rome IV criteria include functional dyspepsia, chronic nausea and vomiting syndrome and centrally mediated abdominal pain syndrome.

Table 3.1 Demographics for the patient population that were given the option of home TENS (N=41).

Patient Characteristics	Male N (%) 5 (12.2)	Female N (%) 36 (87.8)	Total N (%) 41 (100)
Age (Mean, SD)	55.2 ± 11.6	35.5 ± 14.8	42.0 ± 15.2
18-35	0	12	12
35-50	1	11	12
50+	4	13	17
Occupations			
Student	0	6	6
Healthcare	0	5	5
Sedentary Work	1	5	6
Physical Work	0	5	5
Unemployed/ Medical Leave	4	6	10
Unreported	0	9	9
TENS Status			
Active	1	5	6
Discontinued	4	31	35

Risks and contraindications

Non-invasive TENS treatment is low risk for patients (Johnson, 2014, #102539). Stimulation should not be performed over the carotid sinus (neck region) as it may close airways, resulting in difficulty breathing and adverse effects on heart rhythm and/or blood pressure. Stimulation should not be performed trans-cerebrally, nor trans-thoracically, as the introduction of electrical current into the heart may cause cardiac arrhythmias. Treatment should not be performed when driving, operating machinery, or close to water as it may put the patient at undue risk for injury (Roscoe Medical Inc., 2013). There have been reports of skin irritation beneath the area of electrodes. If skin irritation occurs, a different electrode pad will be recommended.

Patients were excluded based on contraindications including pregnancy, cardiovascular diseases, implanted electronic devices (ex. cardiac pacemakers,

implanted defibrillator, etc.), metal implants within application area, sensory disorders, cancer, skin lesions within area of application, psoriasis, scleroderma, viral or bacterial infection, uncontrolled epilepsy, thrombosis, hemorrhage and skin sensitivity or allergies to the electrode adhesive.

Virtual training

All patients underwent a 30-minute virtual training via video call outlining TENS treatment. A formal at-home TENS study protocol was devised and implemented during the virtual training (see Appendix B). The training involved the setting up of the TENS device, including stimulation parameters, information on how to operate the device, placement of electrode pads for targeted treatment, and an experimental trial run of the treatment to provide a sense of what the stimulation feels like. The experimental trial run of the treatment also provided the patient the opportunity to report any immediate concerns or changes in response to the TENS stimulation.

Treatment plan

The TENS treatment plan targets T5-L2 of the thoracolumbar spinal cord (Figure for all patients involved low frequency-high intensity stimulation for 15 minutes, twice a day, for a duration of 4 months.

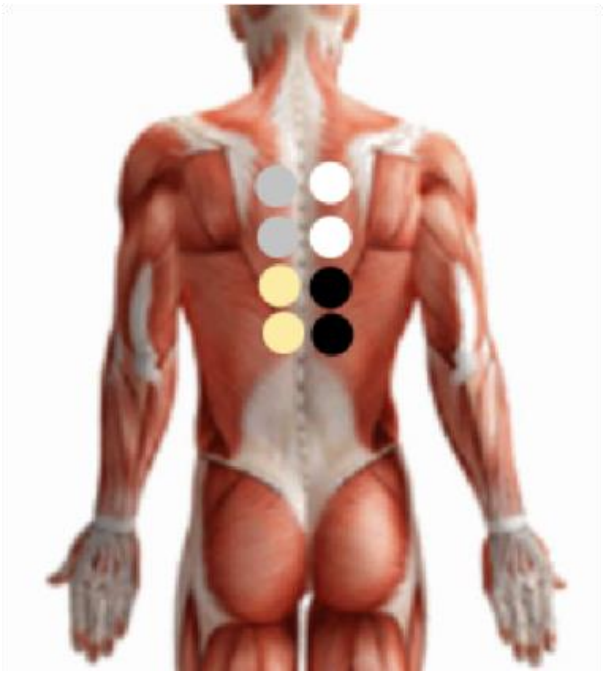

Figure 3.1 Electrode placement of TENS targeting T5-L2.
Each circle represents an electrode pad. Electrodes with the same colour indicate an electrode pair connected to the same channel. The anode electrode is placed above the corresponding cathode electrode for each electrode pair.

Patient-report questionnaire

3.2.1 Objectives and rationale for questionnaire

Patients with upper GI symptoms are asked to complete an online questionnaire involving the assessment of GI symptoms before and during TENS treatment to thoracic and thoracolumbar nerves. Once starting at-home TENS treatment, patients are asked to complete the assessment once every four weeks to re-evaluate both frequency and severity of symptoms. We created the questionnaire to assess whether thoracic neuromodulation treatment has benefited the patient regarding their GI symptoms and with the aim of using results to determine the spinal pathology and symptoms with the most successful response to TENS. Questions are grouped into subgroups based on the location of the symptom and aim to determine the frequency, severity, and characteristics of all GI and neurological symptoms experienced. Frequent re-assessment of patients also allows for the assessment of therapeutic timelines of the TENS treatment, which may be useful when assessing treatment success in future patients. We pay particular attention to compliance and whether or not the patient has changed treatment frequency. We also pay attention to whether or not the treatment as resulted in diminishing of medications. Patients are contacted regularly to clarify questions and responses.

3.2.2 Questionnaire; SEE APPENDIX

3.3 Establishing pathophysiology and success of treatment

Evaluation of the patients who did not enter the study and those who did

Of the 41 patients that were offered home TENS, 15 patients (14 female; 1 male), entered the study and completed 3 or more months of daily TENS (full participation), whereas 7 additional patients (5 female; 2 male), entered the study and completed 1 or 2 months of treatment (partial participation). 19 patients decided to not enter the study (17 female; 2 male) (Fig. 3.2A).

In the 18-35 age demographic most patients entered the study (50% full, 8% partial, 42% did not enter study), followed by the 50+ age demographic (29% full, 29% partial, 41% did not enter study) and the 35-50 age demographic (33% full, 8% partial, 58% did not enter study) (Fig. 3.2B). We analyzed this based on occupation: students (67% full, 33% partial); healthcare workers and those with physically demanding jobs, both 40% full, 20% partial and 40% did not enter study; sedentary work (17% full, 83% did not enter study); and participants who were not currently working due to unemployment or medical leave (25% full, 25% partial, 50% did not enter study) (Fig. 3.2C). The group of subjects whose occupation was unreported were 36% full, 27% partial, and 36% did not enter the study.

The most reported reasons for not entering the study were physical limitation (34%), which subjects reported the electrode pad placements to be too difficult to place

on the thoracic spine on their own, time consumption of the treatment (20%), lack of perceived results (14%), and lack of interest in starting the treatment at all (6%) (Fig. 3.3).

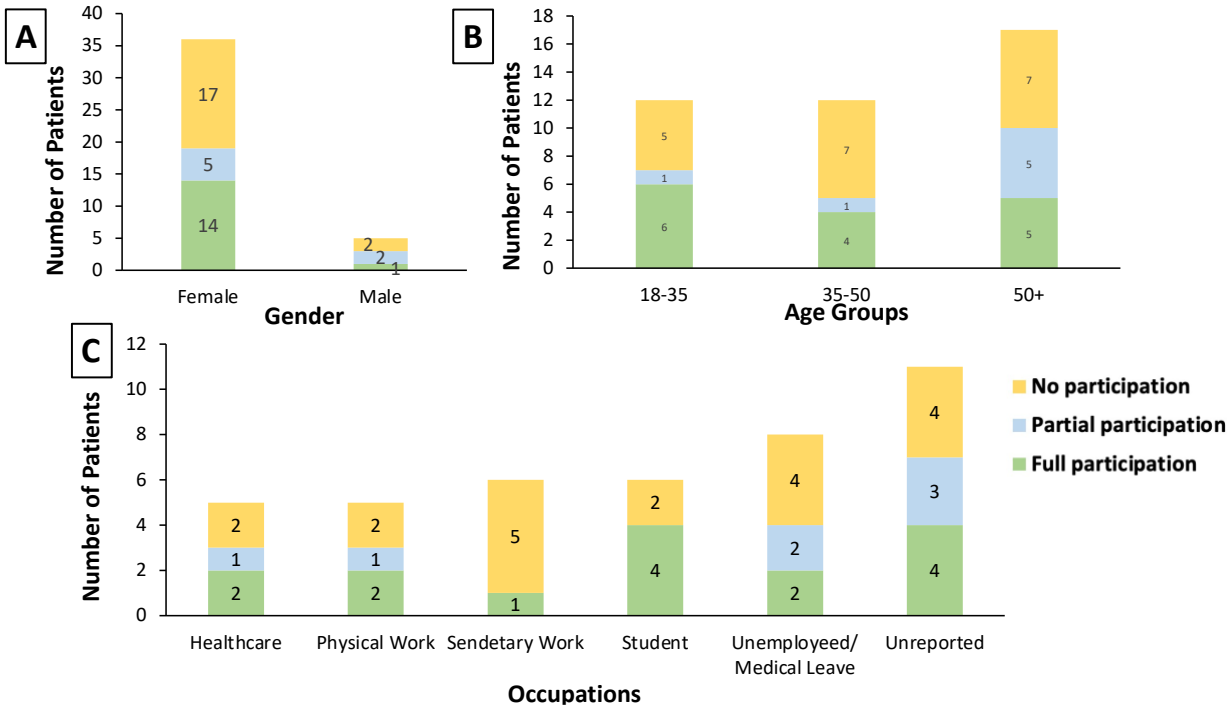

Figure 3.2 Participation analysis based on various parameters.
A – Gender. Female N=35; Male N=5. **B** – Age groups. 18-35 N=12; 35-50 N=12; 50+ N=17. **C** – Occupation. Healthcare N=5; Physical work N=5, Sedentary work N=6; Student N=6; Unemployed/Medical leave N=8; Unreported N=11.

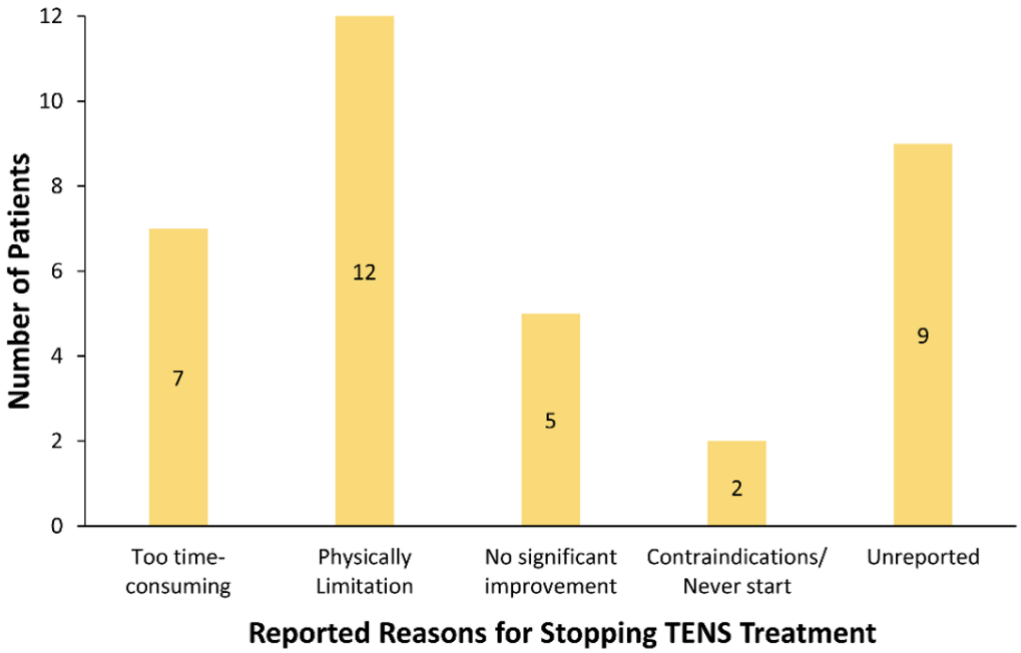

Figure 3.3 Primary reasons for patients to decline or discontinue TENS treatment among those who reported not currently completing TENS treatment (n=35).

Twenty-two patients entered the study; 15 patients completed 3 or more months of TENS whereas 7 patients completed at most 2 months of daily treatment. Of the 15 patents that fully participated 4 completed questionnaires throughout the study and so did 2 patients that partially participated. All other patients completed the questionnaires before the study started and were contacted after they finished the treatment by telephone to complete a follow-up questionnaire. The results of these two groups are reported on separately.

3.4 Results of those patients that completed the questionnaires

Abdominal Symptoms

All the patients reported improvements in the frequency and severity of overall abdominal symptoms, with the exception of one patient who had a consistent score throughout 3 months of treatment (Figure 3.4). This outlying patient reported minimal abdominal symptoms, therefore lack of improvement was considered reasonable. After one month of TENS treatment, all patients with the exception of the outlier saw a minimum of 15% improvement (ranging from 15%-28.9%) from initial assessment. All patients who completed 2 months of treatment reported improvement in abdominal symptoms compared to 1 month of treatment. One patient reported a 2.8% improvement from month 1 (22.2% total improvement from initial assessment), while all other patient reported a minimum of 17.6% improvement from the previous month (ranging from 17.6%-52.2%).

Overall improvement for abdominal symptoms during TENS compared to pre-TENS was seen in all patients.

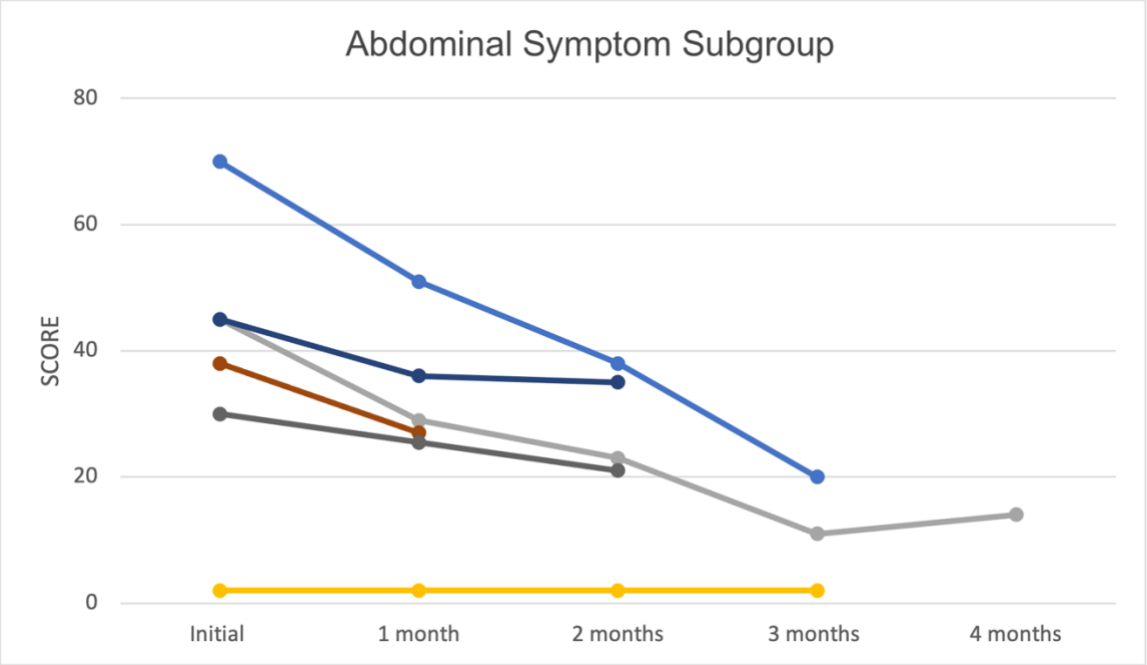

Figure 3.4 Self-reported questionnaire scores for frequency and severity of all abdominal symptoms experienced by patients.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of severe abdominal symptoms in all patients (>20% improvement from initial scores) with the exception of outlier (yellow). Only patients who report exhibiting the symptom are reported in the figure. N=6.

All patients reporting constipation reported severe constipation in their initial questionnaires (N=6). All patients completing at least 2 months of TENS reported improvements from severe to moderate constipation, with the two patients who completed 3+ months of TENS reporting improvements from severe constipation to mild constipation (grey) and absent (orange), respectively (Figure 3.5). 3 patients reported improvements from severe constipation to moderate constipation (N=2) or mild constipation (N=1) after one month of TENS treatment. 2 patients reported no change in constipation severity after one month of treatment, however 2- and 3-month symptom follow up was non-compliant.

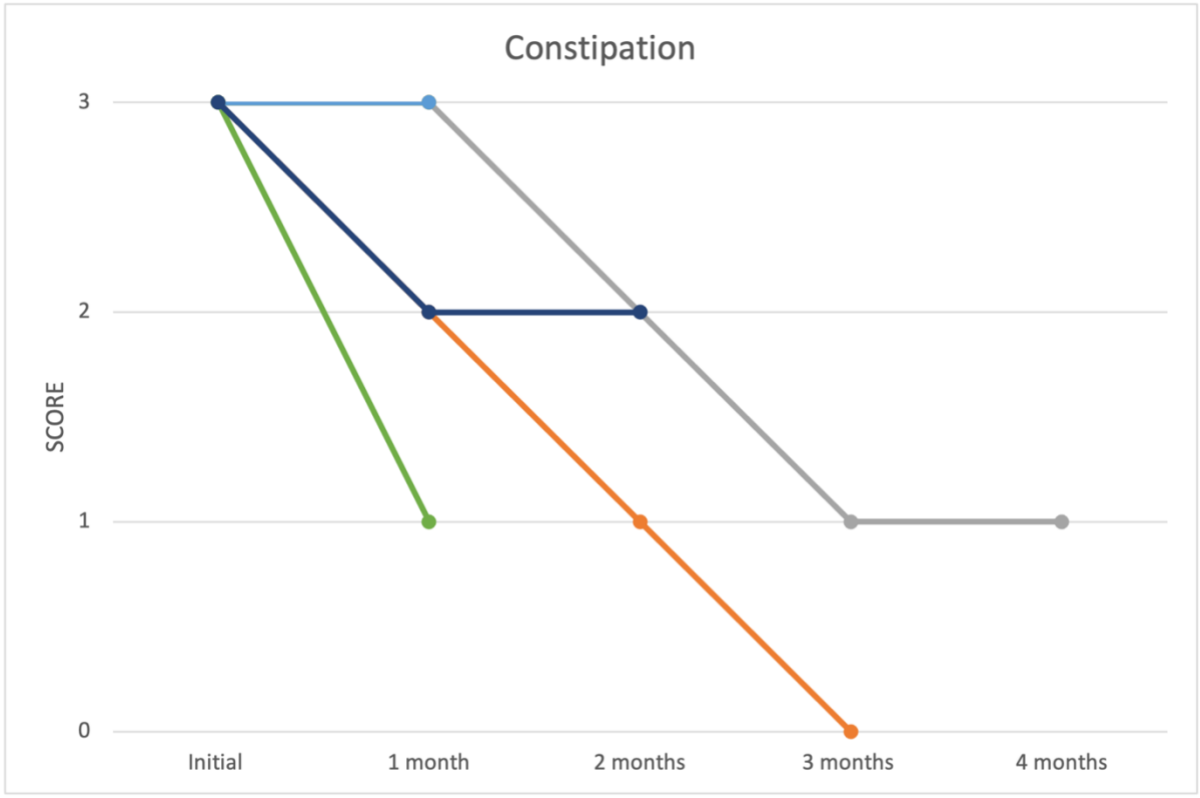

Figure 3.5 Self-reported questionnaire scores for the severity of sudden-onset constipation experienced by patients.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. All patients reported severe constipation in initial scores (N=6). Data indicates success of treatment of constipation in all patients (>20% improvement from initial scores) with at least 2 months of treatment. 3 patients (67%) reported change in constipation severity after one month. Only patients who report exhibiting the symptom are reported in the figure. N=6.

All patients reported improvements in persistent abdominal pain of at least 25% with the exception of one patient who reported a score of 1 (mild persistent abdominal pain) pre-TENS and after 1-month and 2-months of TENS (Figure 3.6). This patient reported the absence of the symptom after 3 months of treatment, which remained absent after 4 months as well. With the exclusion of this patient, all patients who completed 2 months of treatment reported 50%-100% improvement compared to their initial assessment.

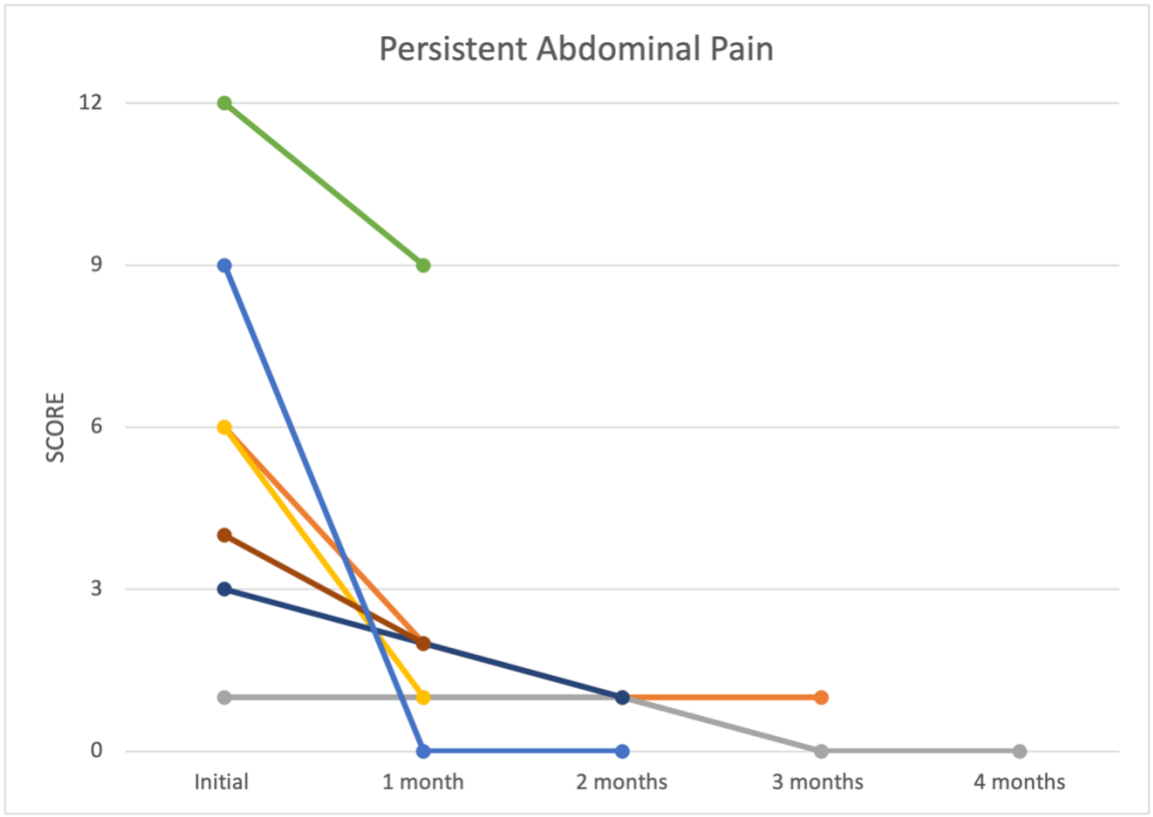

Figure 3.6 Self-reported questionnaire scores for frequency and severity of persistent abdominal pain experienced by patients.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of persistent abdominal pain in all patients (>20% improvement from initial scores) with the exception of one who reported mild persistent abdominal pain until 3-months of treatment (grey). Only patients who report exhibiting the symptom are reported in the figure. N=7.

All patients report a decreased overall score for abdominal discomfort in response to their TENS treatment (Figure 3.6), with the exception of one patient who reported a score of 1 (mild) in the initial assessment and a score of 2 (mild) after one month of TENS. This patient had only completed one month of TENS therefore response to TENS after longer treatment duration is unknown. Another patient reported worsened abdominal discomfort after 1 month of TENS, initially reporting a score of 6 (severe) and reporting a score of 9 (very severe) after 1 month. This patient showed a return to baseline after 2 months of TENS and improvement to moderate discomfort (33% improvement) after 3 months of TENS. This patient also self-reported an increase from *severe* to *very severe* fear and worry and increase from *mild* to *moderate* depression during the first month of treatment. The increased score in abdominal discomfort may be related to increased self-reported mental health symptoms, however, causality is not possible to determine. Other patients report at least 25% improvement in abdominal discomfort after one month of treatment (ranging from 25%-100% improvement) and at least 50% improvement after

two months of treatment (ranging from 50%-100% improvement). The one patient who completed the full 4-month course of treatment reported very severe (score of 9) abdominal discomfort prior to TENS, with improvements for the first three months which sustained at mild discomfort after 4 months of treatment.

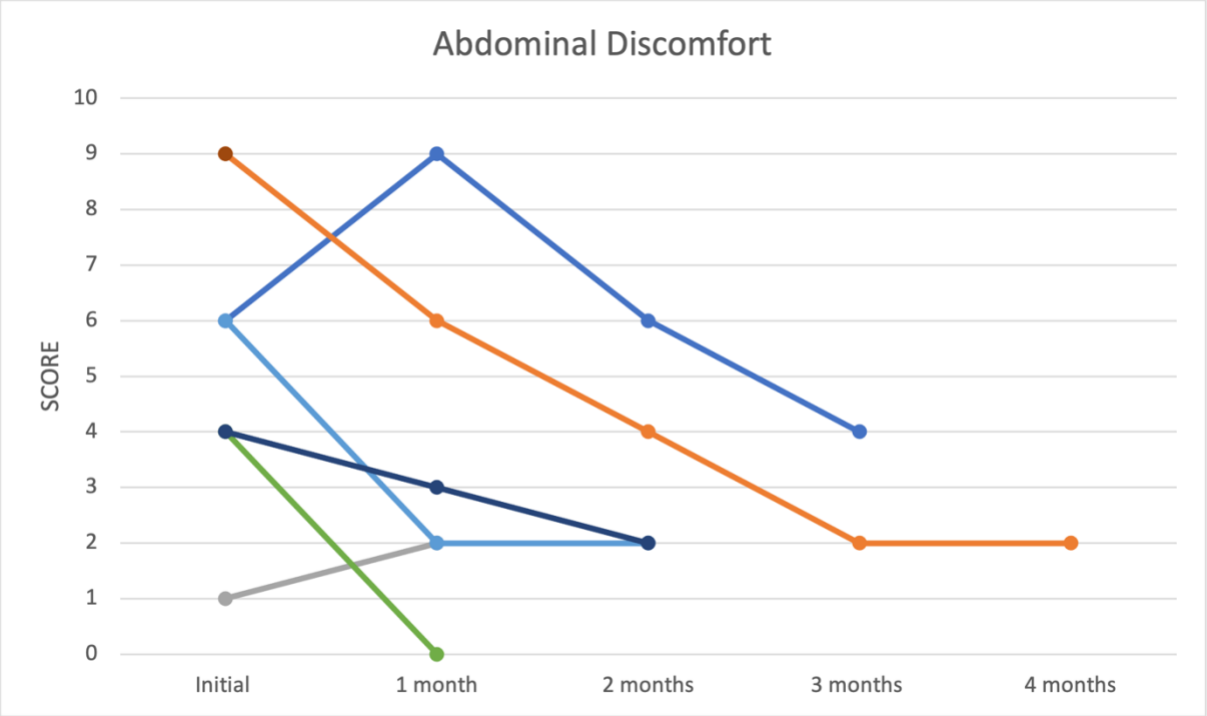

Figure 3.7 Self-reported questionnaire scores for frequency and severity of abdominal discomfort experienced by patients.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal discomfort in all patients (>20% improvement from initial scores) with one patient reporting worsening symptoms after one month of treatment and return to baseline after 2 months of treatment and reporting improvement after 3 months of treatment (blue). Only patients who report to exhibit abdominal discomfort are reported in the figure. N=6.

All patients report improvement in score for abdominal bloating in response to TENS treatment (Figure 3.8). After one month of treatment, all but one patient reported at least 25% improvement in bloating, while after two months of treatment all patients showed at least 50% improvement (ranging from 50%-67% improvement). The two patients who reported very severe bloating prior to TENS reported improvement to mild bloating (score of 2) after three months of treatment. Both patients had spinal pathology of scoliosis at the T10-L2 level.

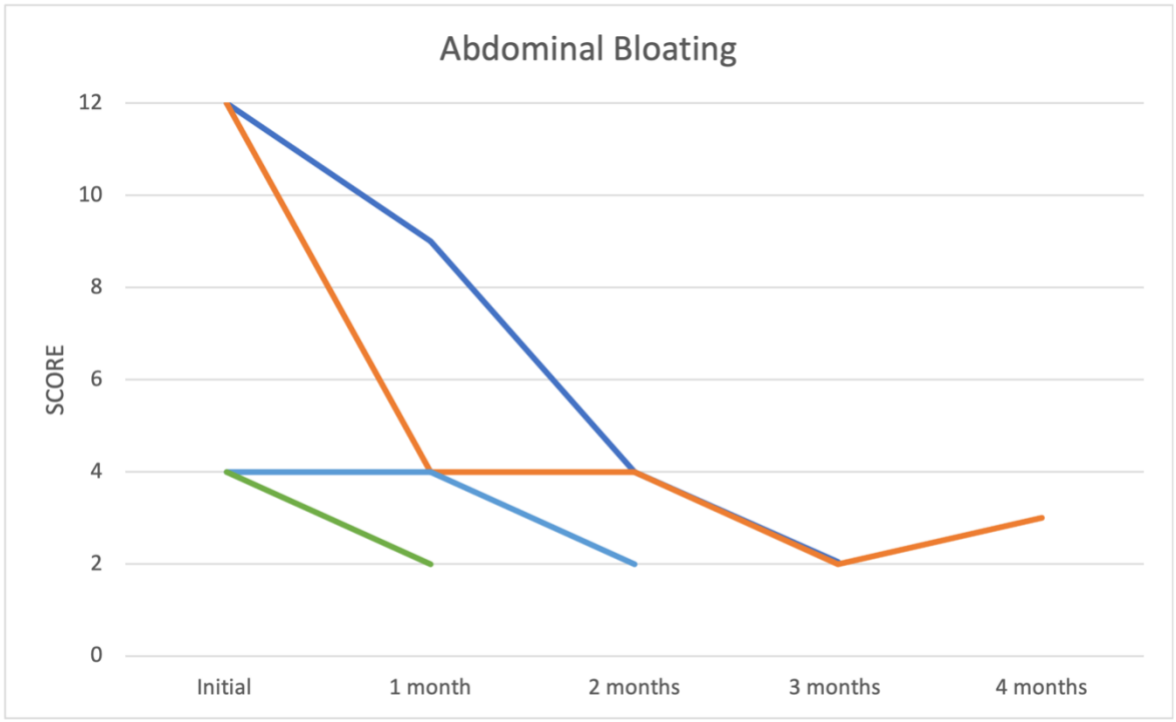

Figure 3.8 Improvements from very severe abdominal bloating to mild abdominal bloating after 3-4 months of TENS treatment.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal bloating in all patients (>20% improvement from initial scores). Only patients who report exhibiting the symptom are reported in the figure. N=4.

Location of Abdominal Pain

All patients report improvements in pain in the generalized abdomen, with the exception of one patient who remained at a score of 1, reporting infrequent, mild pain (Figure 3.9). All other patients have seen at least 33.3% improvement from their initial assessment (ranging from 33.3%-100% improvement). After one month of treatment, one patient reported increased symptoms; this was the same patient that reported increases in abdominal discomfort in this month, as well as increased depression, fear and worry. The increase in reported depression, fear and worry may account for increased abdominal symptoms, however causality is not possible to determine. After 2 months of treatment, this patient reported 33.3% improvement in pain in the generalized abdomen from their initial score and 55.5% improvement from their month 1 score (improvement of *severe* pain to *mild* pain). One patient did not show any change in generalized abdominal pain throughout three months of TENS, however reported only mild, infrequent presentation of the symptom (Figure 3.9). The one patient to complete the entire 4-month duration of treatment reported severe pain in the generalized abdomen prior to TENS, and elimination of the symptom after 3-months of treatment, which remained constant after 4 months of treatment as well.

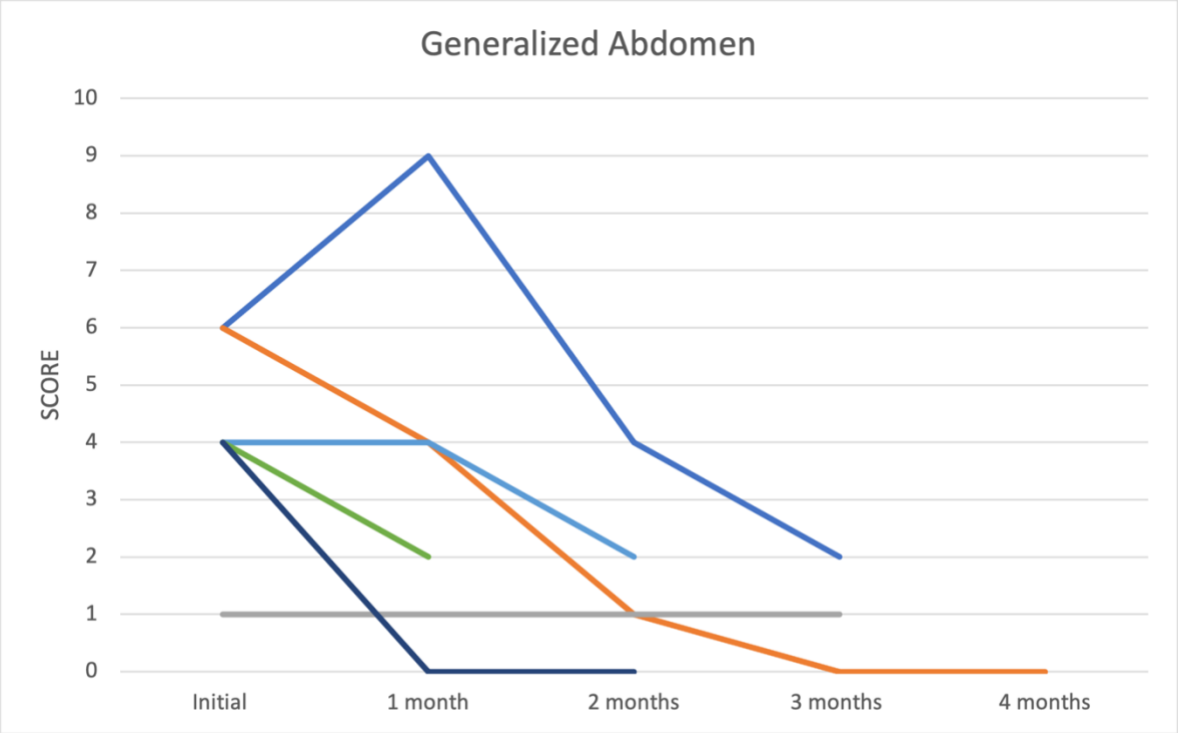

Figure 3.9 Improvements self-reported questionnaire scores for pain in the generalized abdomen in response to TENS treatment.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal pain in most patients (>20% improvement from initial scores), with the exception of one patient who reported mild pain in the generalized abdomen (score of 1) throughout the 3-month duration of treatment. One patient reported elimination of the symptom after 3-months of treatment, which remained absent after 4 months of treatment as well. Only patients who report exhibiting the symptom are reported in the figure. N=6.

All patients, with the exception of one, report improvement of pain in the left upper quadrant in response to TENS treatment (Figure 3.10). All other patients report at least 33.3% improvement (ranging from 33.3%-75% improvement) after one month of treatment. One patient who reported *severe* pain in the left upper quadrant reported improvement to *mild* after 1-month of treatment, which remained consistent throughout the 4-month duration of treatment. One patient reported increased pain in the left upper quadrant, from *moderate* to *severe*, after one month of treatment, however response following this 1-month duration is unreported. One patient reported mild left upper quadrant pain prior to TENS, which was eliminated after 3 months of treatment (Figure 3.10).

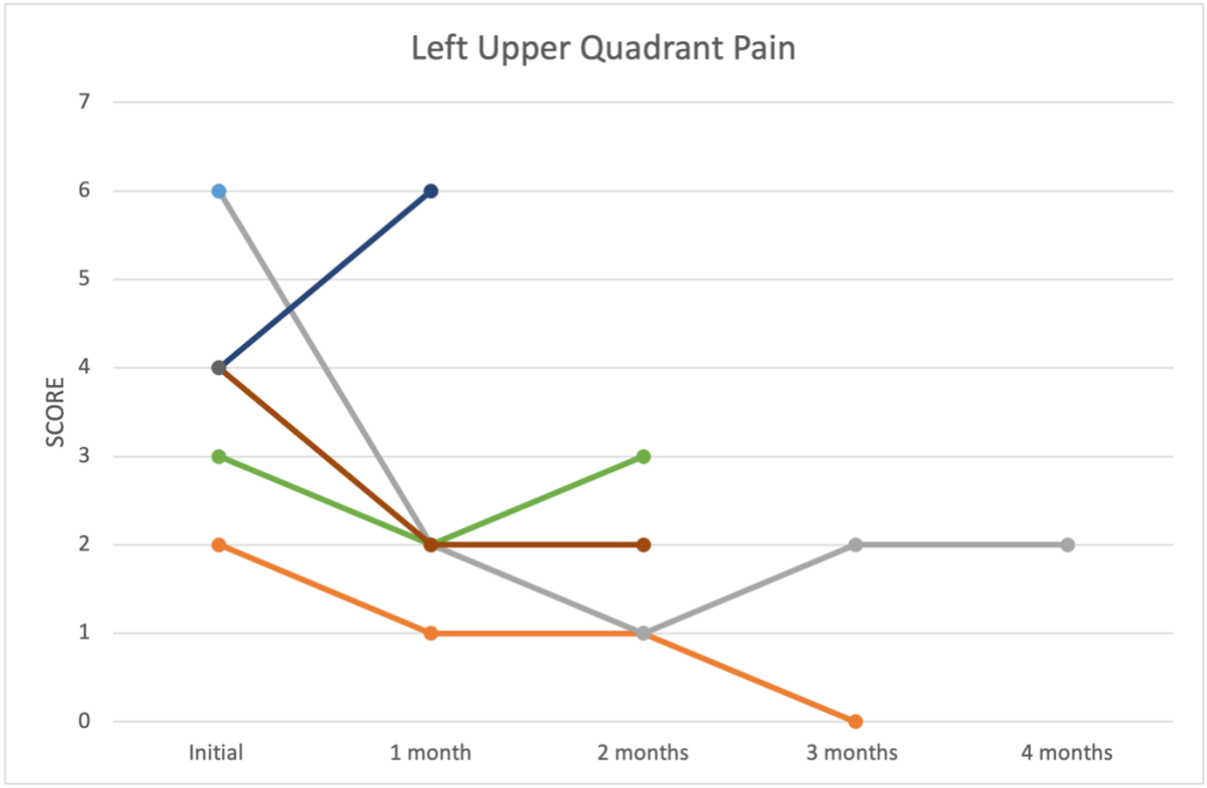

Figure 3.10 Self-reported questionnaire scores for frequency and severity of abdominal pain in the left upper quadrant.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal pain in most patients (>20% improvement from initial scores). One patient reported an increase in score after one month (dark blue). Only patients who report exhibiting the symptom are reported in the figure. N=5.

All patients reporting severe abdominal pain in the left lower quadrant in their initial assessment reported improvements in their pain by the first month of treatment, and continued improvement to mild and absent after 4 and 3 months of TENS treatment, respectively. (Figure 3.11). Both of these patients had spinal pathology of scoliosis at the T10-L2 level. Other patients reporting mild to moderate LLQ pain do not report improvements after 2 and 1 month of treatment, respectively. One patient who had not previously reported the symptom reported to experience mild, infrequent LLQ pain after 2 months of treatment.

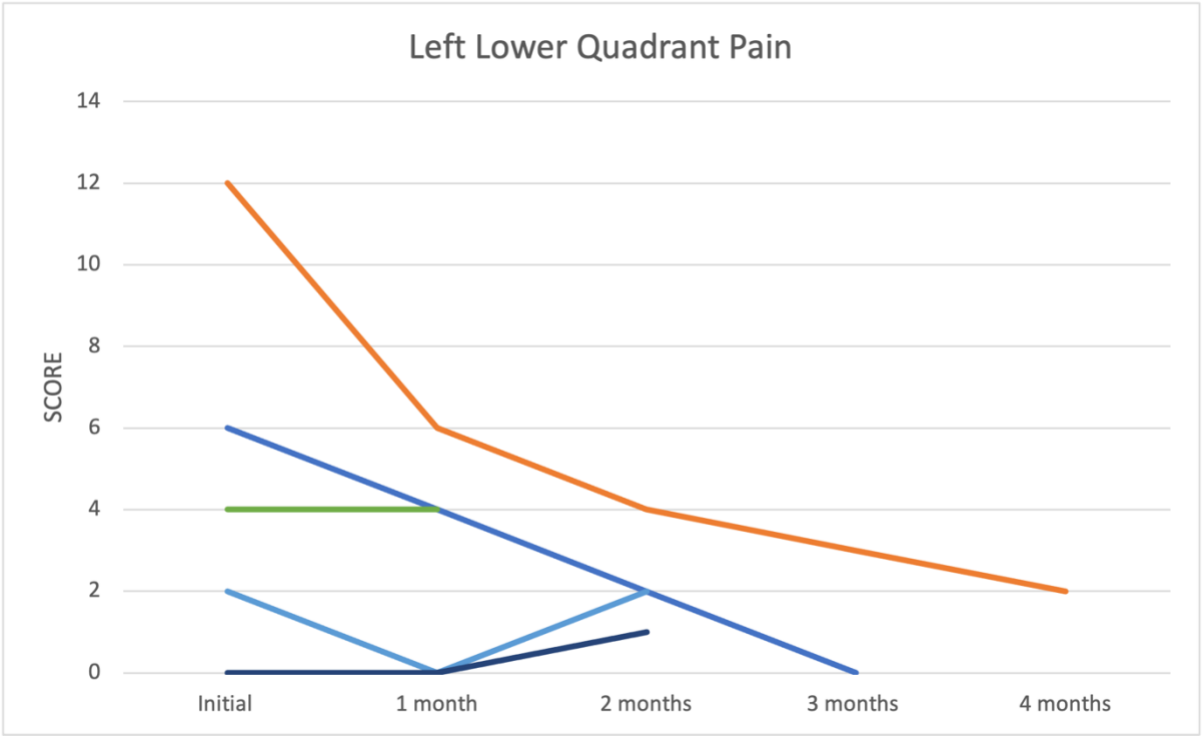

Figure 3.11 Improvements in frequency and severity of pain in the left lower quadrant (LLQ) of the abdomen in response to TENS treatment.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal pain in patients reporting moderate to severe pain prior to TENS treatment (>20% improvement from initial scores). Two patients reporting mild to moderate pain do not report improvement in pain after 2 and 1 month of treatment (green and blue, respectively). Only patients who report exhibiting the symptom are reported in the figure. N=5.

Upper GI Symptoms

All patients reporting nausea reported some improvements in response to TENS treatment. Four patients reporting moderate (score of 4) to very severe (score of 9) nausea all report at least 25% improvement after one month of treatment. One patient reporting severe nausea pre-TENS reported elimination of the symptom after one month of treatment, which remained absent after two months of treatment (Figure 3.12; dark blue). Another patient reporting severe nausea pre-TENS reported improvement to moderate nausea after one month of treatment, and the absence of the symptom after 2 months of treatment (Figure 3.12; light blue). One patient reporting mild nausea pre-TENS reported no presentation of nausea after 2 and 3 months of treatment, however mild nausea again after 4 months. Due to the mild nature of this patient's reported nausea, it is difficult to draw conclusions on the effect of 4 months of TENS on severe nausea from this patient's data.

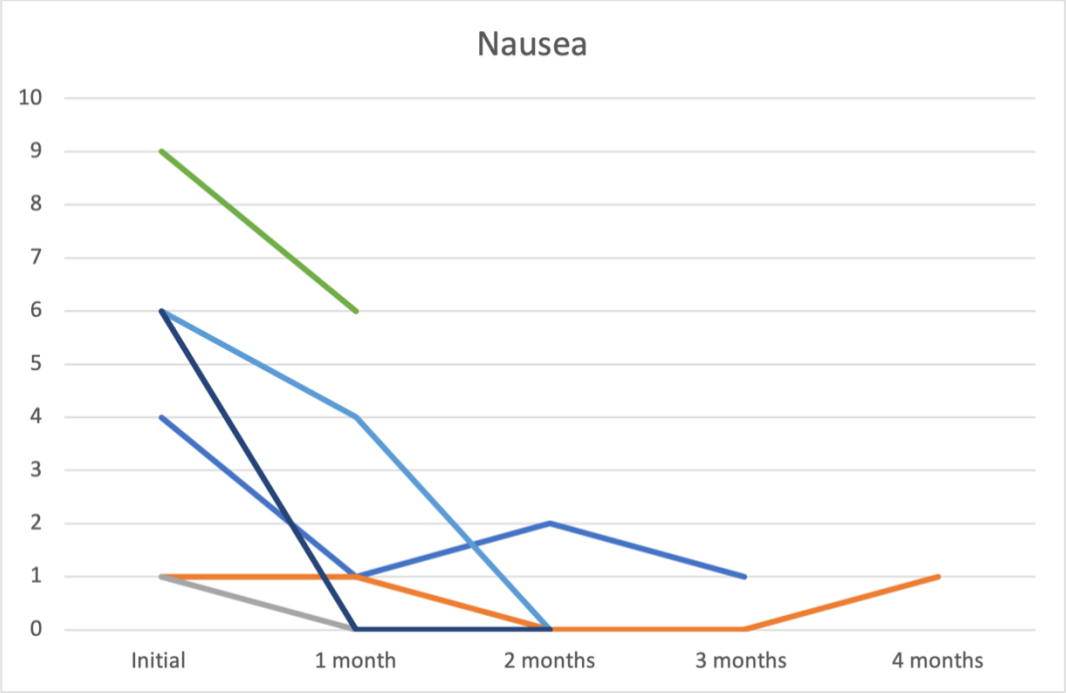

Figure 3.12 . Improvements in frequency and severity of nausea in response to TENS treatment.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of abdominal pain in patients reporting moderate to very severe pain prior to TENS treatment (>20% improvement from initial scores). One patient reporting mild pain (grey) reported improvement in pain after 1 and 2 months of treatment, however reported the return of the symptom (mild) after 4 months of treatment. Only patients who report exhibiting the symptom are reported in the figure. N=6.

One patient reported very severe postprandial hiccups pre-TENS treatment and showed improvements after one month of treatment. After 2 months of treatment, the patient reported experiencing postprandial hiccups again but with only moderate severity, which again were absent after 4 months of treatment (3.12; blue). This patient had scoliosis at the T10-L2 level. Other patients that were compliant with completing TENS treatment/questionnaires reported only mild, infrequent occurrences of postprandial hiccups prior to TENS, which were not eliminated after 1 and 2 months of treatment.

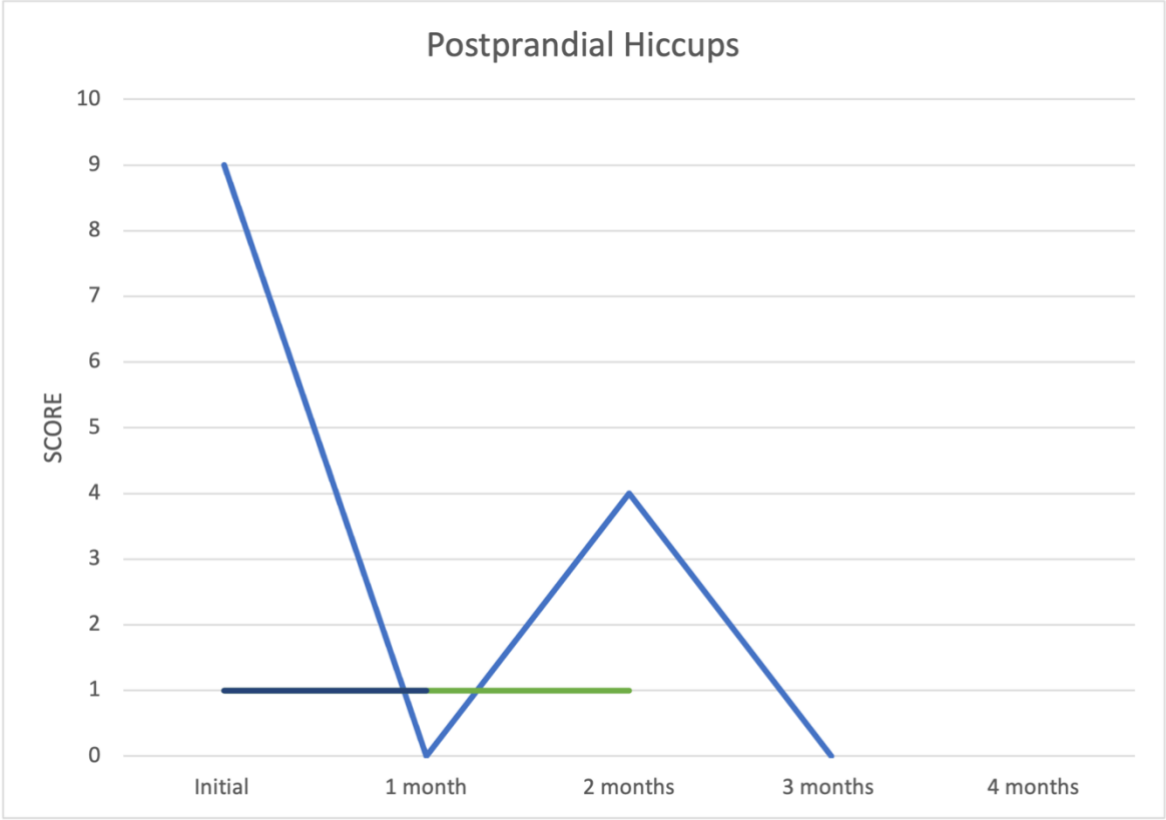

Figure 3.13 One patient showing improvement in score for postprandial hiccups after 3 months of TENS treatment.
Patients reporting mild, infrequent postprandial hiccups (N=2; green and light blue) report no change in frequency or severity of postprandial hiccups after 1 and 2 months of TENS. Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Only patients who report exhibiting the symptom are reported in the figure. N=3.

Two patients report vomiting more than 6 hours after eating, one reporting mild severity and one reporting moderate severity pre-TENS treatment (Figure 3.14). The patient reporting mild vomiting pre-TENS reported vomiting to increase to severe after one month of treatment; this patient had spinal pathology at the T3-T9 level. The patient reporting moderate vomiting pre-TENS reported the absence of vomiting after 1 month of treatment, and mild vomiting after 2 months of vomiting.

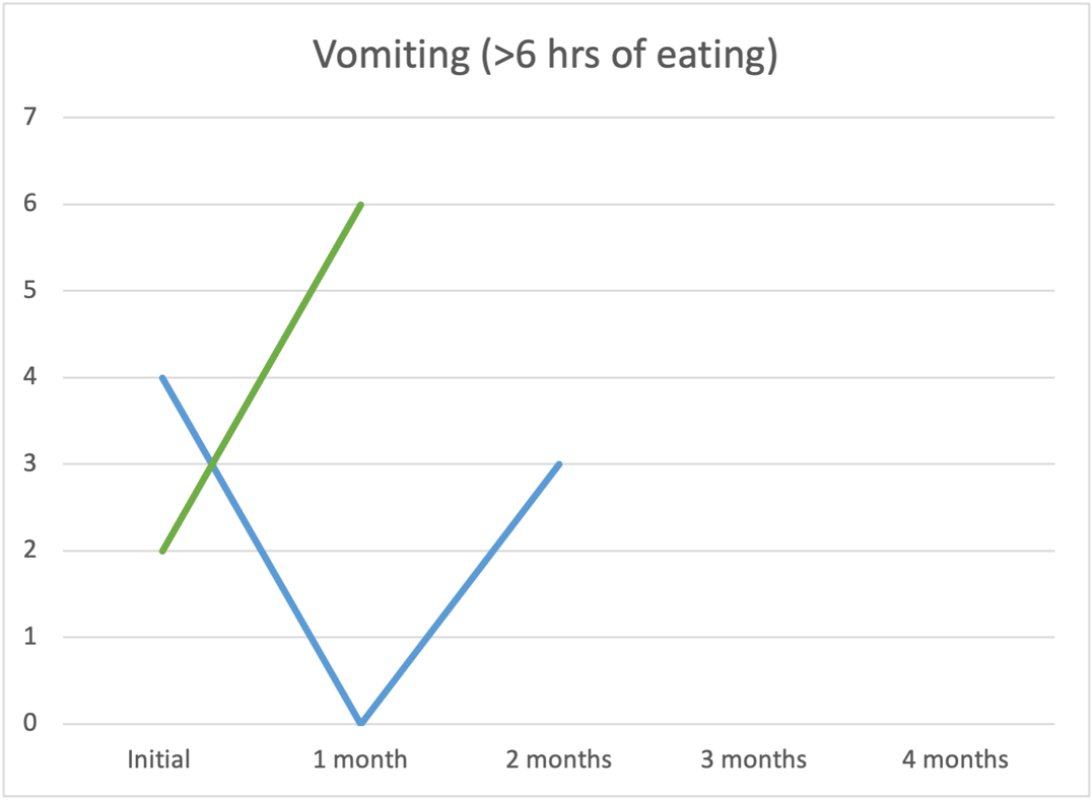

Figure 3.14 Two patients showing change in score vomiting more than 6 hours post-meal after 1 and 2 months of TENS treatment.
Patient reporting moderate vomiting pre-TENS reports absence of vomiting after 1 months of treatment, and mild vomiting after 2 months of treatment (green and blue, respectively). Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Only patients who report exhibiting the symptom are reported in the figure. N=2.

Three patients report regurgitation pre-TENS treatment. Two patients report mild and infrequent regurgitation pre-treatment: one reported worsening of regurgitation to moderate severity after 1 month of treatment, while the other reported no change in regurgitation severity after 2 months of treatment (Figure 3.15). One patient reported moderate regurgitation pre-tens treatment, with reports of the symptom improving to mild regurgitation after one month of treatment but worsening to severe regurgitation after 2 months of treatment.

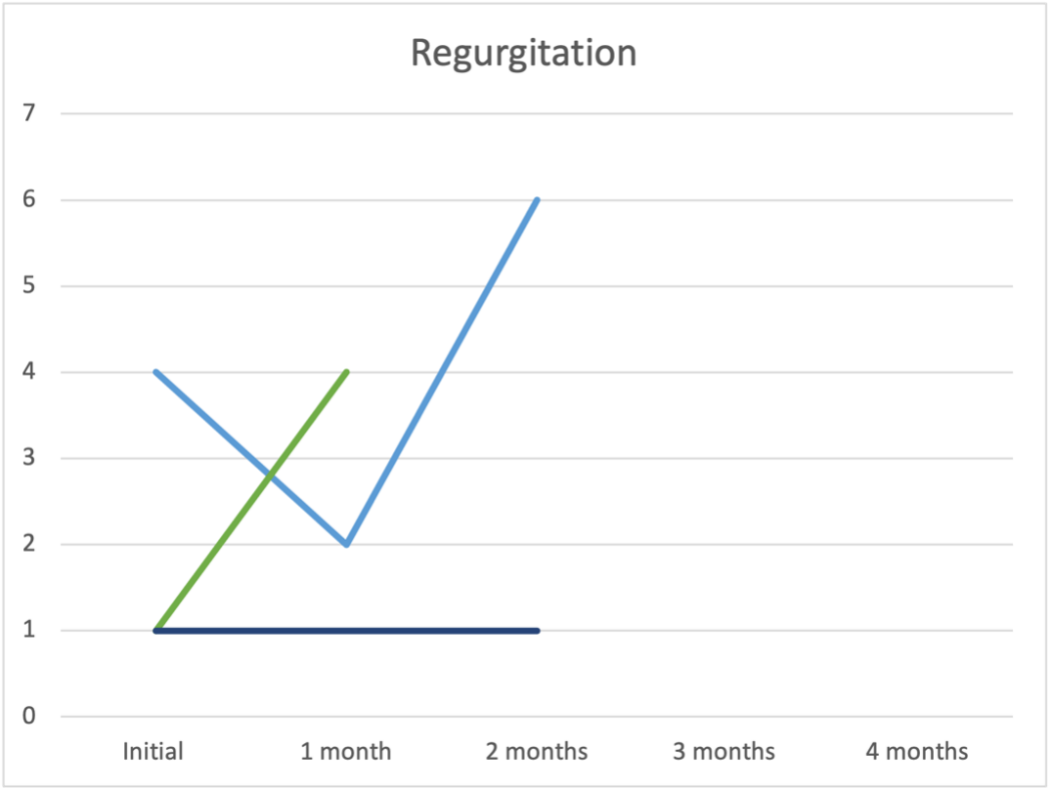

Figure 3.15 Three patients showing change in score for the frequency and severity of regurgitation after 1 and 2 months of TENS treatment.
Two patients reporting mild regurgitation (dark blue and green) report no change in regurgitation symptoms after 2 months and increased severity to moderate after 1 month, respectively. One patient reporting moderate regurgitation pre-TENS reports improvement to mild regurgitation after 1 month of treatment but severe regurgitation after 2 months of treatment. Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Only patients who report exhibiting the symptom are reported in the figure. N=3.

Patients reporting abdominal gurgling showed mixed symptom response to TENS. One patient reported *severe* abdominal gurgling (score of 6) prior to TENS treatment and reported improvements from *severe* to *mild* after 2 months of treatment, continuing to improve to a score of 1 after 4 months of TENS (Figure 3.16). Two patients reported *moderate* severity (score of 4) prior to TENS; one reported improvement to *mild* gurgling after 1 months of TENS while the other reported no response to TENS after one month and worsening of gurgling from *moderate* to *severe* after 2 months. Most patients show some improvement in abdominal gurgling within one month of treatment, and after two months of treatment, most patients show at least 33.3% improvement in abdominal gurgling (Figure 3.16). The two patients showing improvements from severe and moderate gurgling had spinal pathology of scoliosis at the T10-L2 level. The patient who reported worsening of gurgling from a score of 1 to a score of 2 had spinal pathology at the T3-T9 level.

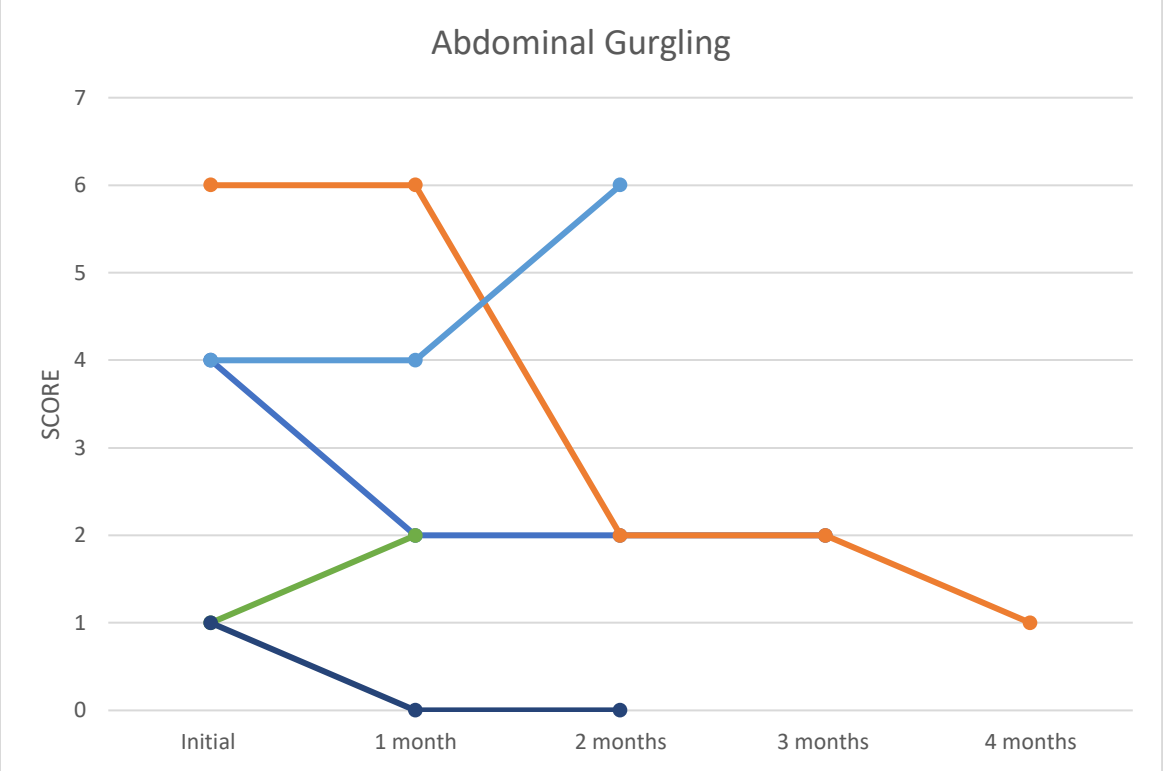

Figure 3.16 Three patients showing improvement in score for the frequency and severity of abdominal gurgling after TENS treatment.
One patient reporting severe abdominal gurgling (orange) reports improvement to mild gurgling after 4 months of treatment, while other patients reporting moderate (N=1; blue) and mild (N=1; dark blue) abdominal gurgling report improvements to mild and absent gurgling after 2 months of treatment, respectively. change in regurgitation symptoms after 2 months and increased severity to moderate after 1 month, respectively. Two patients report worsening of abdominal gurgling after 1 and 2 months of TENS: one increasing from moderate to severe gurgling (light blue) and the other remaining at mild severity (green). Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Only patients who report exhibiting the symptom are reported in the figure. N=5.

3.5 Results of patients that completed questionnaires before and after treatment

The 22 patients who completed full (N=15) or partial (N=7) participation in the study completed the symptom questionnaire twice; once as an initial assessment prior to TENS treatment, and once as a follow-up after discontinuation of the treatment. The treatment start time ranged for all patients, therefore the time of assessment since discontinuation of the treatment was individualized to each patient. Follow-up questionnaires of patients with full participation ranged from 6-12 months post-treatment and follow up questionnaires of patients with partial participation ranged from 8-19 months post-treatment (Table 3.2). The largest improvements in patients were seen in postprandial abdominal pain (93.3% of full participation group, 57.1% of partial participation group),

constipation (70% of full participation group, 66.7% of partial participation group), vomiting (100% of full participation group, 50% of partial participation group), abdominal bloating (72.7% of full participation group, 40% of non-participation group), and nausea (69.2% of full participation group, 40% of partial participation group) (Table 3.4). Improvements were seen more frequently in patients that completed full participation compared to partial participation, particularly in nausea, regurgitation, postprandial abdominal pain, vomiting, abdominal bloating (Table 3.4). Improvements in abdominal pain based on localized region of pain was found to be similar in the full and partial participation groups, except for pain in the generalized abdomen which showed greater improvement in the group with full participation (Table 3.5). The length of time since discontinuation of TENS treatment did not show a large difference on symptom improvements reported by patients in the full or partial participation group.

Table 3.2 Symptom scores of GI symptoms reported by patients' pre-TENS treatment (initial) and post-TENS treatment.

Patient #1-#15 completed full participation of treatment while patient #16-#22 completed partial participation of treatment. Scores highlighted in green indicate ≥20% improvement in the symptom in the post-TENS follow up compared to scores reported prior to treatment. The length of time the patient was compliant with completing TENS treatment and the number of months since TENS treatment at the time of the follow-up assessment indicated for each patient.

	Treatment duration	Time after TENS	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Initial*	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*
Patient #1	3 months	7 months	2	1	2	1	8	6	9	9	0	0	2	1	0	0	0	0
Patient #2	3 months	9 months	9	6	0	0	0	0	0	0	0	0	9	6	9	6	0	0
Patient #3	3 months	11 months	6	1	1	1	0	0	0	0	9	2	9	1	0	0	1	0
Patient #4	3 months	12 months	1	1	12	6	0	0	0	0	0	0	6	0	0	0	0	0
Patient #5	3 months	13 months	4	1	0	0	0	0	9	2	9	0	6	2	12	2	4	2
Patient #6	3 months	16 months	12	4	0	0	12	4	0	0	0	0	9	6	0	0	0	0
Patient #7	3 months	16 months	4	1	6	4	0	0	4	0	6	3	9	2	9	9	6	6
Patient #8	4 months	6 months	0	0	1	1	0	0	0	0	6	3	4	3	6	4	1	1
Patient #9	4 months	12 months	12	12	2	2	12	8	2	2	9	9	12	12	12	12	1	1
Patient #10	4 months	13 months	1	1	0	0	0	0	2	0	9	3	9	4	12	3	6	1
Patient #11	4 months	24 months	6	6	0	0	0	0	0	0	9	9	12	9	9	6	0	0
Patient #12	4 months	24 months	4	0	1	1	4	0	0	0	0	0	6	0	6	0	0	0
Patient #13	5 months	12 months	6	4	2	1	0	0	0	0	9	3	6	4	9	4	0	0
Patient #14	6 months	6 months	9	6	6	2	2	0	0	0	9	9	12	9	12	12	0	0
Patient #15	6 months	12 months	0	0	4	1	1	0	4	4	6	0	9	6	9	0	0	0
Patient #16	2 months	8 months	0	0	1	1	2	2	1	1	9	9	6	4	4	4	1	1
Patient #17	2 months	10 months	12	12	6	6	12	6	2	2	9	9	12	12	12	9	12	0
Patient #18	2 months	10 months	1	0	0	0	0	0	0	0	9	3	8	2	0	0	0	0
Patient #19	2 months	15 months	6	3	4	4	0	0	2	0	9	6	9	9	12	12	0	0
Patient #20	2 months	15 months	4	4	0	0	0	0	9	6	9	6	9	6	0	0	0	0
Patient #21	2 months	19 months	0	0	9	6	0	0	9	6	0	0	9	6	12	9	0	0
Patient #22	2 months	24 months	9	9	0	0	0	0	0	0	9	6	12	12	12	12	0	0

Table 3.3 Symptom scores of different locations of abdominal pain reported by patients' pre-TENS treatment (initial) and post- TENS treatment.

Patient #1-#15 completed full participation of treatment while Patient #16-#22 completed partial participation of treatment. Scores highlighted in green indicate ≥20% improvement in the symptom in the post-TENS follow up compared to scores reported prior to treatment. The length of time the patient was compliant with completing TENS treatment and the number of months since TENS treatment at the time of the follow-up assessment indicated for each patient.

			General abdomen		LUQ		LLQ		RUQ		RLQ	
	Treatment duration	Time after TENS	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Post-TENS*	*Initial*	*Initial*	*Initial*	*Post-TENS*
Patient #1	3 months	7 months	3	1	0	0	2	2	0	0	0	0
Patient #2	3 months	9 months	9	9	0	0	0	0	0	0	0	0
Patient #3	3 months	11 months	0	0	2	0	2	0	9	2	0	0
Patient #4	3 months	12 months	1	0	6	0	6	0	0	0	0	0
Patient #5	3 months	13 months	6	2	2	0	6	0	1	0	6	2
Patient #6	3 months	16 months	9	2	0	0	0	0	0	0	0	0
Patient #7	3 months	16 months	4	2	1	0	6	3	2	0	12	0
Patient #8	4 months	6 months	2	1	0	0	2	2	0	0	2	1
Patient #9	4 months	12 months	12	9	4	4	4	4	0	0	0	0
Patient #10	4 months	13 months	6	0	6	2	12	4	0	0	0	0
Patient #11	4 months	24 months	12	6	12	9	12	9	12	9	12	9
Patient #12	4 months	24 months	0	0	0	0	0	0	0	0	0	0
Patient #13	5 months	12 months	6	4	0	0	6	4	0	0	4	4
Patient #14	6 months	6 months	4	0	0	0	12	9	0	0	12	0
Patient #15	6 months	12 months	9	6	9	6	0	0	9	6	0	0
Patient #16	2 months	8 months	4	2	4	4	4	2	0	0	2	0
Patient #17	2 months	10 months	9	0	12	9	12	0	4	0	4	0
Patient #18	2 months	10 months	0	0	12	4	6	0	0	0	0	0
Patient #19	2 months	15 months	9	9	0	0	0	0	9	9	0	0
Patient #20	2 months	15 months	9	9	0	0	9	6	0	0	0	0
Patient #21	2 months	19 months	9	9	0	0	0	0	0	0	0	0
Patient #22	2 months	24 months	0	0	0	0	0	0	12	9	0	0

NAUSEA	Initial N	Follow-up N (%)
FULL	13	9 (69.2%)
PARTIAL	5	2 (40%)

CONSTIPATION	Initial N	Follow-up N (%)
FULL	10	7 (70%)
PARTIAL	6	4 (66.7%)

REGURGITATION	Initial N	Follow-up N (%)
FULL	10	6 (60%)
PARTIAL	4	1 (25%)

POSTPRANDIAL ABDOMINAL PAIN	Initial N	Follow-up N (%)
FULL	15	14 (93.3%)
PARTIAL	7	4 (57.1%)

VOMITING	Initial N	Follow-up N (%)
FULL	6	6 (100%)
PARTIAL	2	1 (50%)

ABDOMINAL BLOATING	Initial N	Follow-up N (%)
FULL	11	8 (72.7%)
PARTIAL	5	2 (40%)

POSTPRANDIAL HICCUPS	Initial N	Follow-up N (%)
FULL	6	3 (50%)
PARTIAL	5	2 (40%)

ABDOMINAL GURGLING	Initial N	Follow-up N (%)
FULL	6	3 (50%)
PARTIAL	2	1 (50%)

Table 3.4 Prevalence of symptom improvement in full participation group (N=15) and partial participation group (N=7).
Initial N indicates the number of patients reporting the symptom prior to TENS treatment. Follow-up N indicates the number and percentage of patients that reported ≥20% improvement in the symptom in the post-TENS follow up.

GENERALIZED ABDOMINAL PAIN	Initial N	Follow-up N (%)
FULL	13	12 (92.3%)
PARTIAL	5	1 (20%)

RUQ PAIN	Initial N	Follow-up N (%)
FULL	5	5 (100%)
PARTIAL	3	2 (66.7%)

LUQ PAIN	Initial N	Follow-up N (%)
FULL	8	7 (87.5%)
PARTIAL	3	2 (66.7%)

RLQ PAIN	Initial N	Follow-up N (%)
FULL	6	5 (83.3%)
PARTIAL	2	2 (100%)

LLQ PAIN	Initial N	Follow-up N (%)
FULL	11	8 (72.7%)
PARTIAL	4	4 (100%)

Table 3.5 Prevalence of improvement in different locations of abdominal pain in full participation group (N=15) and partial participation group (N=7).
Initial N indicates the number of patients reporting the symptom prior to TENS treatment. Follow-up N indicates the number and percentage of patients that reported ≥20% improvement in the symptom in the post-TENS follow up.

The average change in GI symptom severity scores were also seen to be greater in the full participation group for all symptoms except for abdominal gurgling (Table 3.6). The full participation group particularly reported on average, greater improvement in regurgitation, vomiting, postprandial hiccups, constipation, postprandial abdominal pain and abdominal bloating. Regarding the localization of abdominal pain, pain in the generalized abdomen, LUQ and RUQ showed greater improvements in the full participation group compared to the partial participation group (Table 3.7). Pain in the LLQ and RLQ did not show to be further improved by longer duration of treatment.

Table 3.6 Mean GI symptom improvement (% change) for patients who had completed full participation and partial participation of TENS treatment.

	Full (%)	***Partial (%)***
Nausea	42.2	30
Regurgitation	32.5	8.3
Vomiting	70.8	25
Postprandial hiccups	46.3	26.6
Constipation	51.2	27.7
Postprandial abdominal pain	49.8	24.9
Abdominal bloating	46.6	10
Abdominal gurgling	38.8	50

Table 3.7 Mean pain improvement (% change) in different localized areas of abdominal pain in patients who had completed full participation and partial participation of TENS treatment.

	Full (%)	***Partial (%)***
Generalized abdominal pain	57.9	30
LUQ pain	65.6	30.6
LLQ pain	45.5	70.7
RUQ pain	67.2	41.7
RLQ pain	57	100

3.6 Discussion

Questionnaire results lead us to suggest that neuromodulation of the thoracolumbar spine via TENS may successfully result in the improvement of severe GI dysmotility symptoms and abdominal pain and is a potential treatment for complex GI dysmotility for patients with underlying spinal pathology. We will discuss limitations of this study, but the fact that these patients had suffered for many years with persistent symptoms without finding relief with established treatments leads us to suggest that TENS is a potential treatment and that this study is encouraging to design future studies.

The main symptoms this study found to be affected by TENS treatment are sudden-onset constipation, bloating, persistent abdominal pain, nausea, and abdominal gurgling.

We can predict the spinal groups that TENS would be most successful in based on findings of symptoms related to spinal pathology as discussed in Chapter 2.

Constipation showed improvements in response to TENS treatment. All patients reporting constipation reported severe presentation of the symptom prior to TENS treatment. Three of the six patients reported improvement after 1 month of treatment, while the other three patients reported no change in constipation after one month. One of the three patients reporting no change after 1 month did report significant improvement after 2 and 3 months, resulting in improvement to only mild constipation after their 4 months of treatment, hence, it is reasonable not to see improvements in the two patients who had only provided data after 1 month of treatment. High prevalence of constipation, particularly seen in the T10-L2 scoliosis spinal group (as discussed in section 2.6), it is reasonable to suggest that TENS treatment of the thoracolumbar spine may be a successful treatment for patients with complex GI dysmotility and T10-L2 scoliosis pathology.

Abdominal bloating showed improvements in response to TENS treatment, particularly those reporting severe bloating. Two patients reporting very severe bloating reported improvements to mild after 3 and 4 months of treatment. Both of these patients had scoliosis at the T10-L2, consistent with findings of more severe reports of abdominal bloating in the T10-L2 scoliosis group as discussed in Chapter 2. Other patients with moderate bloating also report improvement to mild presentation of bloating after 1 and 2 months of treatment. We can suggest that TENS may be a successful treatment for bloating, which based on findings in Chapter 2, would be most beneficial for patients with T10-L2 scoliosis, T3-T9 pathology and L2-L5 pathology.

Persistent abdominal pain also showed improvements in response to TENS in all patients. TENS has been used to treat chronic pain for decades, however spinal neurostimulation resulting in improvements in abdominal pain implies the stimulation of neural circuitries involved in the innervation of the gastrointestinal tract that may be impaired due to spinal pathology. One hypothesis is that neuromodulation via TENS stimulates the DRG, which afferent fibres run through from the GI tract in the direction of the CNS. If these circuitries are dysregulated due to spinal pathology, the stimulation of these neural circuitries may regulate them back into a homeostatic state, resulting in the improvement of perceived pain. Due to the high prevalence of abdominal pain in all spinal pathology, we can suggest for TENS to successfully improve abdominal pain in all spinal patients.

TENS treatment showed to improve nausea, particularly for those reporting moderate to severe nausea. Patients reporting mild nausea pre-treatment also saw improvements in the symptom, with the exception of one who reported no overall improvements of their mild (score of 1) nausea after 4 months of treatment. Due to the high prevalence and high severity of nausea in patients with T3-T9- and T10-L2 scoliosis-pathology, we can

suggest that TENS treatment would be successful in treating nausea in all spinal patients, but particularly for T10-L2 scoliosis and T3-T9 pathology.

Abdominal gurgling showed improvements in response to TENS after 2-4 months of treatment. Some patients reported higher scores of abdominal gurgling after 1 and/or 2 months of TENS, however lack of data on continued treatment for these patients make it difficult to interpret what the effect of a full course of TENS treatment would be. Based on the prevalence of abdominal gurgling in patients with T3-T9 pathology, we can suggest that TENS treatment would be a successful treatment suitable for patients with T3-T9 pathology.

It is difficult to draw conclusions from patient data on postprandial hiccups, vomiting > 6 hours after a meal and regurgitation due to lack of reports of the symptoms from the patients who were compliant in completing questionnaires. One compliant patient reported very severe postprandial hiccups pre-TENS and showed improvement to the absence of the symptom after 3 months of treatment. While postprandial hiccups are not highly reported here, we have seen it is a prevalent and potential symptom related to spinal pathology at the T3-T9 level of the spinal cord (see Chapter 2.6). Improvements seen in the one compliant patient reporting severe postprandial hiccups pre-TENS suggests that the TENS may be a promising treatment for the symptom and for T3-T9 pathology, however more data is required to further investigate the effect of TENS on postprandial hiccups.

Only two compliant patients reported vomiting > 6 hours after a meal prior to TENS treatment: one with overall improvement from moderate vomiting to mild vomiting after 2 months of treatment and the other reporting an increase from mild vomiting to severe vomiting after one month of treatment. This patient reporting an increase in score also reported increased scores in abdominal gurgling and reported a stressful event to occurs with increased anxiety, fear and worry. As this patient only reported after on month of treatment and also reported stressful life events that may have been a confounding factor in their response to TENS, it is difficult to draw conclusions from this patient's data. Three patients reported regurgitation prior to TENS; one reporting an increase from mild regurgitation to severe, one reporting improvement from moderate to mild regurgitation after 1 month but worsening to severe regurgitation after 2 months of treatment, and one reporting no change in their mild regurgitation after 2 months of treatment. As none of the patients reporting vomiting > 6 hours after a meal nor the patients reporting regurgitation had completed more than 2 months of treatment, it is difficult to make conclusions surrounding the effect of TENS on vomiting.

There is often fluctuation of the effect of TENS in some patients throughout the multiple months of treatment. This is seen in multiple symptoms, such as abdominal

discomfort, bloating, and postprandial hiccups. It is important to consider multiple factors that could affect symptom response to TENS treatment, such as non-compliance, stress, and anxiety. As treatment duration increased, the more frequently we received reports of decreased compliance of the treatment protocol, such as decreases to only once per day, followed by further decreased to a few times per week, etc. It is also important to consider confounding factors that may affect GI symptoms independent of TENS treatment. Factors such as increased stress and anxiety have been found to have a strong relationship with gastrointestinal symptoms, such as through mechanisms of alterations of the microbiome (Foster & Neufeld, 2013) and through sympathetic activation associated with stress and anxiety (Hoehn-Saric & McLeod, 1988), which is responsible for inhibition of gut motility (Lomax, Sharkey, & Furness, 2010). These factors must be taken into consideration when evaluating symptom response to TENS.

TENS treatment showed improvements in GI dysmotility symptoms and abdominal pain to last as long as 24 months beyond the discontinuation of the treatment. The patient group that completed full participation of the treatment showed higher frequency of improvement and better improvement of severity scores compared to the partial participation group, implying that TENS treatment is most effective when treatment duration lasts at least 3-4 months. Improvements reported by patients in the follow-up assessment were not largely affected by the length of time since discontinuation of the treatment, suggesting that the effect of TENS treatment may last beyond the maximum of 24 months since discontinuation that was reported here. This may also be indicative of treatment compliance playing an important role in the effect of TENS treatment. The exact frequency of treatment and whether the treatment protocol was accurately followed throughout the duration of their treatment was not reported and may have significant impact treatment results. This information would be required in future studies to accurately assess the effect of TENS on GI symptoms. This study also did not have data outlining whether the patients reporting no improvement in symptoms in their follow-up assessment reported any improvements throughout the time of their treatment. This information would be required to determine the effect of TENS immediately after treatment versus the effect of TENS beyond the discontinuation of treatment.

Improvement in abdominal pain supports the idea of TENS stimulating sensory pathways and afferent fibres (A-δ) involved in the nociception of pain from the periphery to the central nervous system through the stimulation of the DRG (see figure 1.2) while improvements in GI dysmotility symptoms controlled by autonomic pathways, such as nausea, constipation, bloating and abdominal gurgling, lasting beyond discontinuation of the treatment support the idea of TENS stimulation allowing for homeostatic return for dysregulated spinal circuitries involved in spinal pathology-induced GI motility. Based on study findings, we can suggest that TENS treatment is suitable for thoracolumbar spinal

pathology induced-GI dysmotility, particularly in pathology from T3-T9 (due to improvements in nausea and abdominal gurgling) and T10-L2 (due to improvements in constipation, bloating, persistent abdominal pain and nausea). We can infer that TENS neuromodulation may also be beneficial for non-spinal-induced autonomic dysfunction-related GI dysmotility, however this needs to be further investigated.

Questionnaire

The questionnaire successfully allowed for the assessment of symptom response to TENS treatment through monthly re-assessments. The extensive nature of the questionnaire allowed the monitoring of pathological and neurological symptoms to best predict the symptoms with the most successful response to TENS. This, in combination with the suggested symptoms indicative of spinal-induced GI dysmotility, also allowed for the prediction of which spinal pathology and GI symptoms TENS treatment would be best suited for, however further investigation is required with a larger sample size. The use of this questionnaire in the future of clinical assessments would allow not only the suggestion of spinal pathology based on symptoms, but also indicate whether the patient is likely to be best suited for successful TENS treatment. It acts as an efficient guide for clinicians and physicians in the diagnosis process, while also brining the benefit of ensuring the treatment is best suitable for the patient's individual condition.

Placebo effects

The issue of placebo on the effects of TENS treatment is valid and debated in the neuromodulation literature. Systematic reviews of TENS treatment have concluded that TENS treatment is superior to placebo TENS for improvement of pain and nausea and vomiting (Johnson, 2017). Based on the improvements seen in our study on severe GI dysmotility thus far, as well as the long duration of symptoms experienced by patients with previously failed treatment attempts, such as pharmacological treatment, we hypothesize the success of TENS treatment on thoracolumbar spinal nerves. Further studies are needed to assess the role of placebo effects on thoracolumbar TENS treatment.

Problems with including a placebo trial for 4 months

The tingling sensation associated with the stimulation of TENS results in challenges when considering the inclusion of a placebo trial. TENS is commonly used in physiotherapy and for at-home use, resulting in many people being familiar with it. The lack of sensation during a placebo or sham treatment will provide insight into the study group in which a patient is in, threatening the integrity of the single-blind trial. The TENS treatment is also an at-home, self-performed treatment, therefore it is difficult for a control

group to self-perform the treatment without being aware of the device or stimulation being turned on.

Hesitation to take part in the study involved physical limitations, time consumption and lack of perception of treatment success. These issues will also be relevant for a placebo trial. The lack of stimulation sensation, which in the treatment group may contribute to the encouragement of patient compliance, may further increase hesitation to participate due to lack of perception of treatment success and decrease the encouragement for patients to continue treatment regardless of physical difficulties or time consumption.

Placebo controlled trials in the literature

Moore et al. conducted a randomized clinic trial looking at the effects of transabdominal inferential electrical stimulation in women with functional constipation with a sham stimulation (Moore, Gibson, & Burgell, 2020). The active inferential stimulation involved the passing of currents diagonally through the abdomen while the sham therapy involved the passing of currents subcutaneously (running laterally). 53% of the treatment group met the primary goal of ≥3 spontaneous bowel movements per week, while only 12% of the sham group met the same primary goal, indicating that the treatment effectively reduced constipation in women. The use of an active placebo accounted for issues accompanying a placebo with the absence of stimulation, which may cause doubt in plausibility due to lack of stimulation sensation. The active sham was concluded as an effective placebo with little to no impact on constipation-related symptoms.

He et al. investigated the effects of TENS on abdominal and back pain associated with pancreatic cancer in a randomized, single-blind, controlled trial (He et al., 2021). A TENS group was provided electrical stimulation twice per day for a duration of 1-week, while a sham group had the treatment device set up on them (electrodes placed on body and connected to device) without stimulation. The study found the TENS group, compared to the sham group, to have pain significantly controlled without analgesic medication, showing effects of improving abdominal and back pain lasting 3 weeks beyond the discontinuation of treatment. Patients in both groups also reported constipation and/or poor appetite prior to treatment. 100% of patients in the TENS group who exhibited constipation reported improvements after treatment and 91% of patients in the TENS group who exhibited poor appetite reported improvements after treatment. No patients in the sham group with constipation and/or poor appetite reported improvements after the treatment.

Rakel et al. conducted a study aiming to determine the degree of placebo that is associated with a new transient sham TENS device versus an inactive sham (no

stimulation sensation at all) when looking at pain thresholds (Rakel et al., 2010). With the transient sham TENS, the device delivered a current for the first 30 seconds of treatment, ramped down to zero stimulation over the next 15 seconds, then remained off for the duration of the treatment. The transient sham blinded 40% of participants compared to the active placebo, which only blinded 21% of participants. This patient population however did exclude any patients who reported prior use of TENS. The study also found that the 45-second stimulation from the sham treatment did not result in significant changes to the pain thresholds reported by patients, suggesting the success of finding a placebo that accounts for participant doubt surrounding inactive sham (non-stimulation) but also does not have a significant effect on the treatment outcome.

Ideal protocol design(s) including placebo

The most ideal protocol design including a placebo would involve a sham TENS such as the one used in Rakel et al., involving a sham device that delivers a small current that ramps down to zero stimulation, increasing the blindness of the study and accounting for the issue of no stimulation in the sham group implying they are receiving the placebo. This ideally would be best suited for an in-clinic daily treatment to improve the challenge of compliance associated with at-home treatment and confirm that stimulation parameters and electrode placements are accurate. This was not a reported issue in the at-home study, however the common reports of physical difficulties or limitations by participants can lead us to consider the potential prevalence of incorrectly administered treatment. The protocol used by Rakel et al. involved the exclusion of participants who had previously used TENS, however due to our study population of participants with spinal conditions, many patients reported previous experience/use of TENS for their back pain either through physiotherapy or at-home use. It would be difficult to include this exclusion criteria, therefore, looking into options of blinding the treatment name, such as referring to the treatment as ‘neuromodulation’ rather than specifying that the treatment is from a TENS device, may allow for the elimination of this exclusion criteria in our protocol. Having participants travel to the clinic for in-person daily treatment is not efficient, nor realistic for a 4-month duration, so this treatment protocol will need to be modified, including a potential change in timeline. Most patients who entered the study did not exceed 3 months of treatment, therefore looking into a 2–3-month treatment duration may improve full participation. Another significantly reported reason for discontinuation of treatment was physical limitation or challenge placing electrode pads on the thoracic spine. Ideally, the development of a device or unique equipment to place the pads in the appropriate positions would likely improve participation by accounting for physical limitation, and also improve user error that may occur due to incorrect electrode placement. Due to reports of lasting effects of TENS beyond the discontinuation of TENS treatment, a study design including 6-month, 1-year, and 2-year follow ups of conditions and the effects of TENS would be beneficial to determine the long-term effects of TENS treatment. This addition

to the study protocol will allow for the investigation of the hypothesis of TENS stimulating neural circuitries in patients in allostasis, leading to prolonged therapeutic effects due to reactivation of neural circuitries back into their homeostatic state.

Looking into a practical and feasible study design, issues surrounding the use of a placebo leads to the idea of a study with a 4-month period of treatment involving standard diet and lifestyle changes, followed by a 4-month period of TENS treatment, with the aim of the additional 4-month period of lifestyle/diet treatment to account for some of the placebo associated with treatment in general. Follow ups would be conducted after 6 months, 1 year and 2 years to assess the effect of TENS beyond the discontinuation of the treatment and further test the hypothesis of neuromodulation reactivating neural circuitries back into their homeostatic state. Monitoring of the autonomic nervous system via HRV parameters at the time of each symptom assessment (prior to TENS, once per month during treatment, and at each post-TENS follow up) would also allow for the monitoring of the effect of TENS on autonomic function and autonomic pathways involved in GI motility. Further involvement from family at the time of treatment training may assist in the reported issues of physical limitations to complete the treatment, while the implementation of a patient treatment booklet or diary for the patient to log daily treatment may prompt patients to complete the treatment more regularly and also provide researchers with more information on the effect of TENS specifically based on treatment frequency.

Limitations

In addition to the lack of a placebo, this study has several limitations, including small sample size and the self-report nature of the questionnaire. The self-reporting aspect of the questionnaire can result in response bias, causing some inaccuracy in reported data. The number of patients reporting questionnaire data was small (N=7), with N numbers for each group often smaller due to lower reports of some symptoms. Of the patients that entered the study, only one patient completed the entire 4 months of treatment and one completed 3 months of treatment. The remaining 5 patients were only somewhat compliant, reporting 1-2 months of treatment. This limits the integrity of findings due to lack of data on the true effect of TENS for the entirety of the treatment protocol. The at-home nature of the treatment also resulted in lack of compliance of completing the treatment twice a day as described in the protocol. Treatment frequency was often reported to decrease as the total duration of the treatment progressed, resulting in limited integrity of data on symptom response, particularly in the latter months. We therefore cannot make accurate inferences on the most effective timeline of TENS treatment, such as when the treatment shows the most significant effects on symptoms.

Conclusion

Success of thoracolumbar TENS treatment in complex GI dysmotility symptoms, including potential symptoms related to spinal pathology in complex GI dysmotility patients opens the door to the development of treatment targeting primary pathology in attempt to gain the best patient outcome. It can be concluded that the questionnaire effectively monitored GI and neurological symptoms both prior to and during TENS treatment, allowing for the evaluation of symptom response to TENS. Study results, in addition to thoracolumbar TENS providing a safe, non-invasive treatment option for complex GI dysmotility, warrants further investigation of the effects on complex GI dysmotility, including the investigation of differences in TENS response based on the region of spinal pathology and type of pathology (type of spinal condition) to determine the patients and pathology that would be most benefited by thoracolumbar TENS treatment.

4 Case Reports on Two Patients

Abstract

This case report highlights the relationships between spinal pathology and gastrointestinal symptoms in two patients, including complex GI dysmotility symptoms and pain, and to show results of home-based thoracic transcutaneous electrical nerve stimulation. Both patients exhibit cases of complex GI dysmotility symptoms and severe abdominal pain with thoracic pathology due to scoliosis at the T10-T12 level. After 3 and 4 months of TENS neuromodulation treatment, both cases reported improvements in dominant GI symptoms including sudden-onset constipation, severe postprandial abdominal pain and abdominal bloating, with improvements lasting 9-10 months beyond the discontinuation of treatment. The correlation between localized abdominal pain with GI dysmotility and the thoracic spine innervation is unclear, however symptom presentation and improvements in response to TENS implies spinal nerve pathology-related visceral pain and GI dysmotility causing impairment of the somatic-visceral and autonomic pathways present at the thoracolumbar spinal level. Further clinical observations are required, given the important roles of the innervated organs such as upper GI tract and the diaphragm. The diagnostic and therapeutic values of non-invasive neuromodulation using TENS in these cases highlight this dark corner between gastroenterology and neurology.

4.1 Introduction

Gastrointestinal (GI) dysmotility disorders can be challenging and complex to diagnose, and the pathophysiology of many conditions is poorly understood. Patients with unremarkable GI investigations lack clear GI diagnosis other than ‘functional GI disorder’, resulting in severe abdominal pain, difficulty of oral food intake, and frequent hospitalizations with a lack of effective pharmacological treatment. It is common to see a history of spinal conditions or spinal injury in patients with undiagnosed symptoms of GI dysmotility, leading to the possibility of spinal nerve-related pathology, particularly conditions of the thoracolumbar spine, leading to neurogenic impairment (see Chapter 2.7.1).

We aim to investigate the treatment of complex dysmotility patients with spinal conditions via thoracolumbar spinal neuromodulation to better understand the pathophysiological relationship between dysmotility and abdominal pain symptoms and spinal condition and the effect of TENS treatment on GI dysmotility symptoms. Here we report two cases of patients with complex GI dysmotility symptoms and severe abdominal

pain with scoliosis at the T10-L2 level of the thoracolumbar spine, who underwent 3-4 months of TENS neuromodulation treatment.

TENS treatment allows for a non-invasive form of nerve stimulation for therapeutic action (Moore et al., 2018) that is easily accessible and low-cost (see Chapter 3.2). The TENS treatment protocol in the following cases involved neurostimulation of the thoracolumbar spine from T5-L2 with aim of stimulating somatic-visceral communication and sympathetic pathways to treat GI dysmotility and severe abdominal pain (see Chapter 3.1 for treatment protocol). Both patients underwent TENS treatment, intended to be completed for 15 minutes, twice per day for a 4-month duration. Case #1 completed three months of TENS treatment and was compliant with completing questionnaires, however decreased treatment to once per day 3-5 times per week in months 2 and 3 (Table 4.1). Case #2 completed the entire 4-month treatment plan, however decreasing treatment frequency to once per day in the second month (Table 4.1).

Table 4.1 TENS treatment compliance in case #1 and case #2

	1 month	***2 months***	***3 months***	***4 months***
Case #1	Twice per day	Once per day 3-5 days/week	Once per day 3-5 days/week	Stopped TENS
Case #2	Twice per day	Once per day	Once per day	Once per day

4.2 Case #1

Patient Presentation

This female patient suffered with severe abdominal pain, abdominal bloating, and chronic constipation of a 5-year duration, with worsening progression of a 2-year duration. Abdominal pain presented as sharp with cramping and occurred mainly in the generalized abdomen and right and left lower quadrants of the abdomen. Generalized abdominal pain lasted all day with moderate severity. Right and left upper abdominal pain was dull, lasting 1-2 hours. Pain in the left upper quadrant was sharper than in the right upper quadrant, occurring more frequently and lasting longer. Lower abdominal pain presented as severe, sharp and crampy, lasting around 5 hours and worsening at night. Pain in the right lower quadrant was often sharper than pain in the left lower quadrant. All experienced abdominal pain had no clear triggers and occurred both post-prandially and not. The pain very frequently radiated to the lower back, presenting as a dull but severe pain. The patient had intermittent flare ups of severe attacks of sharp abdominal pain with associated excessive sweating and blurry vision. Additional symptoms exhibited include symptoms of the mouth, throat and chest, such as frequent heartburn, throat tightness, globus sensation, esophageal spasm, and severe post-prandial hiccups.

Past History

The patient has past medical history of GERD, anxiety, chronic fatigue with brain fog, chronic joint pain and chronic lower back pain without clear reason, and query syncope due to a previous syncopal attack. The patient is active and previously participated in competitive sport involving repetitive and vigorous motion, however reported some improvement in abdominal symptoms and constipation after stopping this activity.

Diagnostic Imaging

X-ray imaging of the spine indicated scoliosis, showing a mild curve in the lower thoracic spine (approximately T10-T12) and a significant curve in the lumbar spine. The cervical spine also showed to be strained.

Abdominal MRI revealed dilation of the colon with haustral shape intact. Both an MR enterography and colonoscopy showed to be unremarkable.

Diagnostic hypothesis prior to TENS

Systemic disorders such as celiac disease or inflammatory bowel diseases were initially suspected. Inflammatory bowel diseases such as Crohn's disease or ulcerative colitis were ruled out via an unremarkable MR enterography and elimination of gluten from their diet saw no resulting improvements in their symptoms or condition. Small intestinal bacterial overgrowth (SIBO) was also suspected however no improvements in symptoms or condition resulted from antibiotic treatment.

There is the potential for curvature of the thoracolumbar spine to induce spinal nerve impingement and lead to symptoms of the gastrointestinal tract. Given patient history of scoliosis, vigorous sport and partial improvement of symptoms after discontinuation of participation in the sport, patient symptoms may be related to spinal pathology.

Therapeutic Approach: TENS

Due to the X-ray findings of scoliosis in the thoracic and lumbar spine, our hypothesis was that thoracolumbar spine nerve neuropathy may induce abdominal symptoms such as abdominal pain caused by hypersensitivity of spinal afferent neurons and bloating caused by general inhibition of intestinal motility (Malagelada, Accarino, & Azpiroz, 2017). Over-excitation of the sympathetic nervous system caused by spinal conditions at the thoracic spine may be related to the inhibition of GI motility, leading to bloating. If this is

the case, the patient may benefit from therapeutic neuromodulation of the thoracic spinal nerves. The patient has completed at-home daily TENS treatment of the thoracolumbar spine.

Effects of TENS: Symptom Monitoring

One month

After one month of twice daily TENS treatment of the thoracolumbar spine, the patient showed overall improvements in the frequency and severity of head, neck, shoulder, mouth/throat, chest, abdominal, and back/spine symptoms (Figure 4.1). Improved frequency of constipation from very frequent (>60% of the time) to frequent (30-60% of the time) and improved frequency of additional symptoms such as nocturnal abdominal pain. Improved frequency and severity of symptoms such as persistent abdominal pain, abdominal cramping and early satiety. Improved severity of symptoms such as abdominal bloating and abdominal gurling. There was complete improvement in symptoms such as esophageal spasm, post-prandial hiccups and nausea/vomiting associated with abdominal pain. The patient had decreased frequency of left upper quadrant pain from 1-2 hours to less than an hour, and decreased frequency of left lower quadrant pain from 5 hours to an hour. Improvements were shown in both frequency and severity of right lower quadrant pain, from very frequent and moderate to infrequent and mild. Pain radiating from the abdomen to the upper and lower back, shoulder, neck, jaw, legs and pelvic region showed no improvements. Pain radiating from the abdomen to the chest showed improvement in frequency.

Two Months

After two months of TENS treatment of the thoracolumbar spine, the patient showed overall improvements in the frequency and severity of head, shoulder, mouth/throat, chest, abdominal, and back/spine symptoms (Figure 4.1). There were further improvements in overall head symptoms, mouth/throat symptoms, abdominal symptoms, and pain radiating from the abdomen since the 1-month mark of treatment. Constipation further improved in frequency to ‘infrequent’, compared to ‘very frequent’ prior to TENS treatment. Further improvement was seen in frequency and severity of abdominal bloating, from very frequent and very severe prior to treatment, to frequent and moderate after two months. Abdominal pain in the left upper quadrant improved from lasting 1-2 hours, to lasting a few minutes at a time. Abdominal pain in the right lower quadrant and left lower quadrant pain frequency from 5 hours to 1 hour. Previous sharp pain in lower quadrants is now a crampy pain. Improvements were seen in the severity, from severe to moderate, of pain radiating to the lower back and the legs. Pain radiating from the

abdomen to the shoulders, chest and neck showed complete improvement (did not occur).

Three Months

After three months of TENS treatment of the thoracolumbar spine, the patient showed further improvements in the frequency and severity of head, neck, mouth/throat, chest, abdominal, and back/spine symptoms compared to the two-month mark. (Figure 4.1). Constipation further improved, with the patient reporting the absence of constipation after 3 months of treatment. The patient also reported the absence of abdominal pain in the right upper quadrant (RUQ), the left upper quadrant (LUQ) and left lower quadrant (LLQ) (Table 4.2). Pain in the generalized abdomen was reported to remain dull and decreased from all day presentation to less than 3 hours, with improvement to mild severity. Pain in the right lower quadrant remained as a cramping sensation for approximately 1-hour duration, however reported frequency improved to infrequent, and severity improved to mild (Table 4.2). Overall, improvements were reported in upper GI symptom such as postprandial hiccups, nausea, throat tightness, heartburn, abdominal gurgling, and esophageal spasm.

Table 4.2 Features and questionnaire scoring for location of abdominal pain in case #1

	Initial	**1 month**	**2 months**	**3 months**
Generalized Abdomen	All day Cramping, burning	All day Dull	All day Dull	≤ 3 hours Dull
	Questionnaire Scoring:			
Frequency *Severity*	Very frequent Severe	Very frequent Very severe	Frequent Moderate	Frequent Mild
Right Upper Quadrant	Dull ≥ 1 hour	Sharp ≤ 1 hour	Dull ≤ 1 hour	Absent
	Questionnaire Scoring			
Frequency *Severity*	Infrequent Mild	Frequent Moderate	Frequent Mild	Absent
Left Upper Quadrant	Dull, sharp 1-2 hours	Dull Less than hour	Sharp Few minutes Random onset	Absent
	Questionnaire Scoring			
Frequency *Severity*	Frequent Mild	Infrequent Mild	Infrequent Mild	Absent
Right Lower Quadrant	Sharp, crampy 5 hours Worse at night	Sharp, tender Short BM helps	Cramping 1 hour BM helps	Cramping 1 hour BM helps
	Questionnaire Scoring			
Frequency *Severity*	Very frequent Moderate	Infrequent Mild	Frequent Moderate	Infrequent Mild

Left Lower Quadrant	Crampy 5 hours Worse at night	Sharp, Tender Short BM helps	Crampy 1 hour BM helps	Absent
	Questionnaire Scoring			
Frequency *Severity*	Very frequent Moderate	Frequent Moderate	Infrequent Moderate	Absent

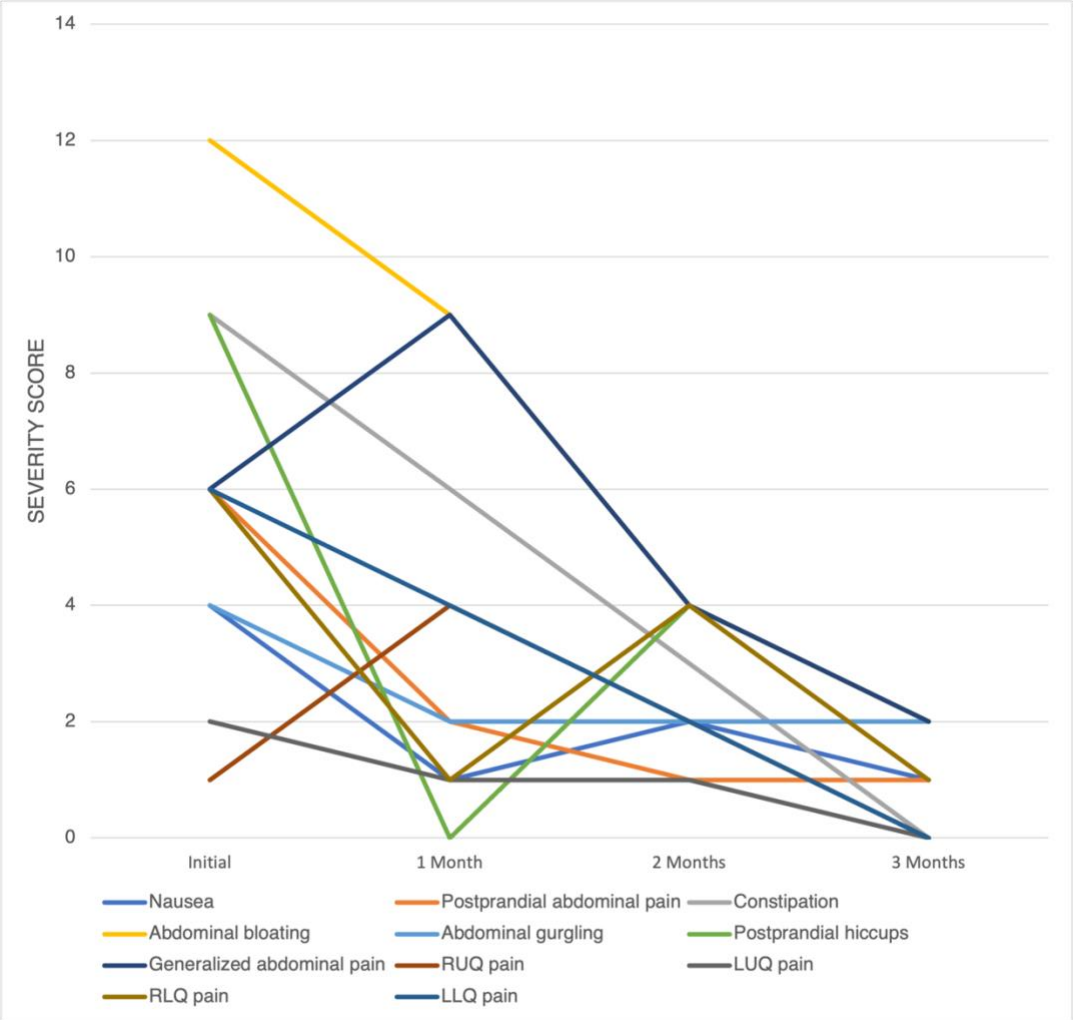

Figure 4.1 Symptom response to TENS treatment throughout three months of treatment in patient #1.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of GI dysmotility symptoms (>20% improvement from initial scores) after 2 months of treatment. 2 months into TENS, treatment shows 83% improvement in persistent abdominal pain, 56% improvement in abdominal cramping, 67% improvement in abdominal bloating, 56% improvement in early satiety, 33% improvement in generalized abdominal pain, 50% improvement in abdominal pain in the left upper quadrant, 67% improvement in abdominal pain in the left lower quadrant, 33% improvement in abdominal pain radiating to the lower back, 56% improvement in postprandial hiccups, and 100% improvement in esophageal spasm.

In a follow up 13 months after beginning TENS treatment, the patient reported to have completely discontinued all treatment since the 3-month treatment duration (10 months after discontinuation of the treatment). The patient reported symptom scores that remained at the improved score (Figure 4.2). Nausea, abdominal bloating, abdominal gurgling, postprandial hiccups, generalized postprandial abdominal pain remained at the same score as directly after 3 months of treatment (all reported as *mild*). Constipation and pain in the LLQ, LUQ and RUQ remained absent. The patient reported one increase in severity score; pain in the RLQ, which increased from a score of 1 (*mild*) after 3 months of treatment to a score of 2 (*mild*) 10 months after discontinuation of the treatment.

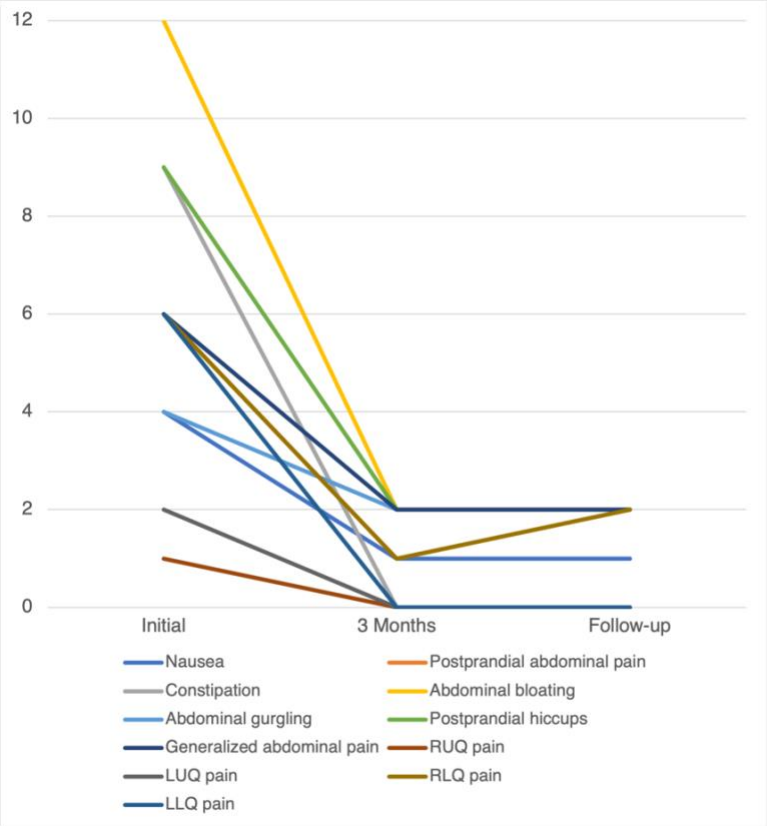

Figure 4.2 Symptom improvements lasting 10 months after discontinuation of TENS treatment for Case #1.
Graph indicates symptom scores reported prior to TENS treatment, after 3 months of treatment, and in a follow-up 10 months after discontinuation of the treatment. Symptom improvement shown to last beyond the discontinuation of the treatment.

4.3 Case #2

Patient Presentation

A female patient suffered with chronic constipation and associated abdominal pain in the left lower quadrant, epigastric area and left upper quadrant, with a severe fullness sensation lasting 4-8 hours postprandially. Constipation was reported to be very frequent with a 9-year duration; without daily laxative, stool was type 1-2 on the Bristol stool chart with no bowel urgency. The patient reported one bowel movement every 3-4 days with laxative but would go up to 2-weeks without a bowel movement. Postprandial abdominal

pain occurred most frequently in the left lower quadrant with feelings of severe pressure and associated bloating, but also occurred in the left upper quadrant, epigastric area and generalized abdomen with similar features. Abdominal pain was often associated with lower back pain. Abdominal gurgling was also reported in the left lower quadrant of the abdomen.

Past History

The patient has a history of urinary incontinence and has had falls with tailbone/spinal injury throughout her life. She experiences chronic pain in the lumbar spine, possibly related to previous injury.

Diagnostic Imaging

Upper endoscopy and colonoscopy both were unremarkable. Anorectal manometry and balloon expulsion test both showed to be normal, indicating normal anorectal motility. A SHAPE study used to measure colonic transit found no evidence of obstruction and showed results of mild colonic dysmotility.

Spinal X-ray showed scoliosis at the thoracic spine with mild curvature at T12. X-ray also showed grade 2 spondylolisthesis of L5-S1, and irregular curvature and increased bone density of the coccyx.

Autonomic Testing

The patient underwent testing of the autonomic nervous system via HRV parameter analysis prior to beginning TENS treatment. Testing was complete with the aim of analyzing autonomic function and reactivity. The patient underwent measurement of the parasympathetic nervous system (via RSA) and the sympathetic nervous system (via SI) with a protocol involving measurement at supine (baseline), sitting, standing, then sitting again. This patient's baseline autonomic functioning is within the normal range but shows sympathetic dominance (Figure 4.3). Going from supine to sitting is normally associated with an increase in sympathetic and a decrease in parasympathetic activity, in this patient, the opposite occurred although the values remained within the normal rage. The reactivity to standing was a strongly exaggerated sympathetic activation combined with an exaggerated reduction in parasympathetic activity. The overall shift that can be expressed as SI/RSA shows a very strong shift into the sympathetic domain. It is clearly associated with the act of standing since the recovery is strong. This data warrants the hypothesis that the overexcitation can be associated with other body functions that elicit an autonomic response. The urge to defecate should result in excitation of the parasympathetic system and a decrease in sympathetic activity. It may be that the urge

in this patient is accompanied by sympathetic over-excitation, but our data do not prove this.

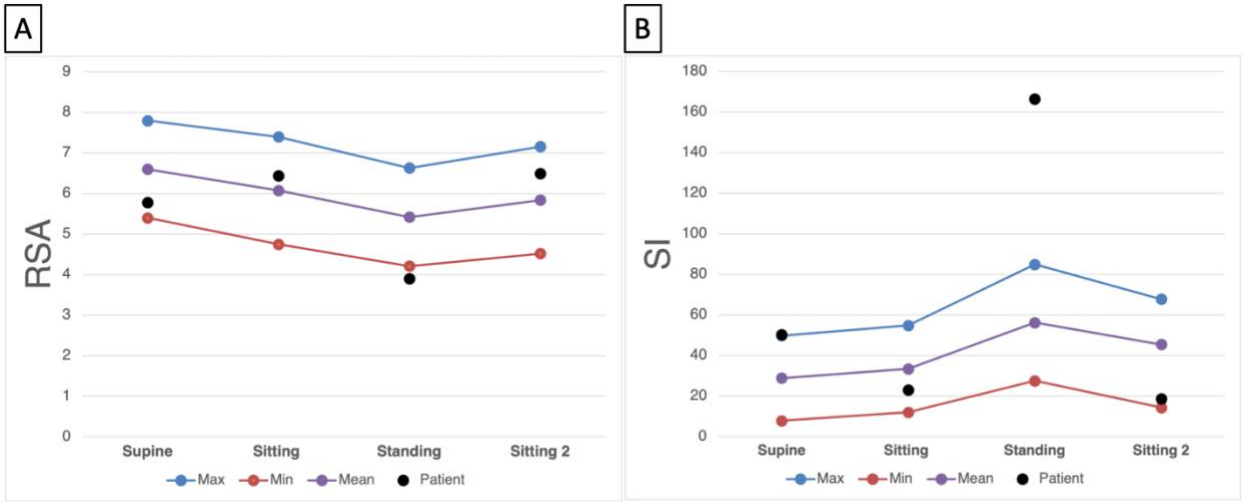

Figure 4.3 HRV findings of patient #1 in autonomic assessment via supine-to-standing test. Mean indicates mean values of normal controls. Maximum indicates mean + 1SD of normal controls, minimum indicates mean - 1SD of normal controls. **A.** RSA measurement in supine-to-standing test assessing parasympathetic tone and reactivity. **B.** SI measurement in supine-to-standing test assessing sympathetic tone and reactivity.

Diagnostic hypothesis prior to TENS

A previous SHAPE study showed positive results, showing delayed colonic transit. A balloon expulsion test was negative, ruling out functional outlet obstruction. High resolution colonic manometry showed absence of significant propulsive motor patterns (high amplitude pressure waves, or HAPWs) in the distal colon.

Combination of scoliosis at T12 and coccyx injury may cause extrinsic nerve-related neuropathy, causing GI symptoms. Neuropathy at the T12 level may impair sympathetic innervation to the colon and further inhibit transit, or cause dysregulation of the sensory afferent pathways involved in the innervation of the GI tract, possibly involved in experienced upper GI symptoms such as epigastric pain, epigastric gurgling and nausea. Previous coccyx injury may impair sacral spinal nerves involved in parasympathetic innervation of the colon, possibly involved in colonic dysmotility symptoms such as constipation. The history of urinary incontinence experienced by the patient may also be attributed by T12 pathology, as the least splanchnic nerve that arises from T12 contributes to the sympathetic innervation of the renal plexus (McCausland & Sajjad, 2021).

Therapeutic Approach: TENS

Due to scoliosis present at T12, it is possible that thoracic spine nerve neuropathy may induce GI dysmotility symptoms experienced by the patient, such as abdominal pain caused by hypersensitivity of spinal afferent neurons, abdominal bloating and chronic constipation. Over-excitation of the sympathetic nervous system caused by the spinal curve located at T12 may be responsible for symptoms of inhibited gastrointestinal and colonic motility. If this is the case, the patient may benefit from therapeutic neuromodulation of the thoracic spinal nerves.

Effects of TENS: Symptom Monitoring

The patient has undergone 4 months of TENS neuromodulation treatment on the thoracolumbar spine. After 2 months of TENS treatment, the patient reported the new spontaneous urge to defecate, which she reports to had not experienced before. She reported significant improvements in constipation, with several days in a row with spontaneous bowel movements with stool at a type 4 on the Bristol stool chart and only infrequent constipation.

After 4 months of treatment, the patient reported constipation and postprandial abdominal pain to be significantly improved. After 4 months, she reported frequent spontaneous urge to have a bowel movement, with type 4 stool based on the Bristol stool chart, usually every other day, and discontinuation of a calcium antagonist medication due to symptom improvement and no longer requiring. Improvements included persistent abdominal pain (100% improvement), abdominal gurgling (83% improvement), abdominal bloating (75% improvement), abdominal fullness with increased gas production (50% improvement), postprandial pain in the generalized abdomen (100% improvement), LUQ (67% improvement) and LLQ (83% improvement). While still reporting significant improvements compared to pre-TENS symptoms, the patient reported increases in score for some abdominal symptoms compared to the third month of treatment. The patient reported increases in abdominal symptoms such as intermittent abdominal pain, abdominal bloating, and abdominal fullness with increased gas production, however all remained in the mild-moderate range. The patient also reported significantly higher scores of symptoms involving the head (Figure 4.4) after month 4, compared to improvements of head symptoms seen in months 1-3. Some increased scores include anxiety and worry, both being reported in the *severe* range (Figure 4.5).

Table 4.3 Features and questionnaire scoring for location of abdominal pain in case #2

	Initial	**1 month**	**2 months**	**3 months**	**4 months**
Generalized Abdomen	Fullness, high-pressure pain 4-8 hours Worse post-prandial, laying down helps	Fullness, high-pressure pain 4-8 hours Worse post-prandial, laying down helps	Fullness, high-pressure pain Few hours Worse post-prandial, laying down helps	Absent	Absent
	Questionnaire Scoring:				
Frequency	Frequent	Very frequent	Infrequent		
Severity	Severe	Moderate	Mild	Absent	Absent
Left Upper Quadrant	Fullness, pressure 4-8 hours No triggers	Fullness, pressure 4-8 hours No triggers	Fullness, pressure Few hours No triggers	Fullness, pressure Few hours No triggers	Fullness, pressure Few hours Laying down helps
	Questionnaire Scoring				
Frequency	Frequent	Infrequent	Infrequent	Infrequent	Infrequent
Severity	Severe	Moderate	Mild	Moderate	Moderate
Left Lower Quadrant	Sharp, bloating 4-8 hours Laying down helps	Sharp, bloating 4-8 hours Laying down helps	Bloating, fullness Few hours Laying down helps	Bloating, fullness Few hours Laying down helps	Bloating, fullness Few hours Laying down helps
	Questionnaire Scoring				
Frequency	Very frequent	Very frequent	Frequent	Infrequent	Infrequent
Severity	Very severe	Moderate	Moderate	Severe	Moderate

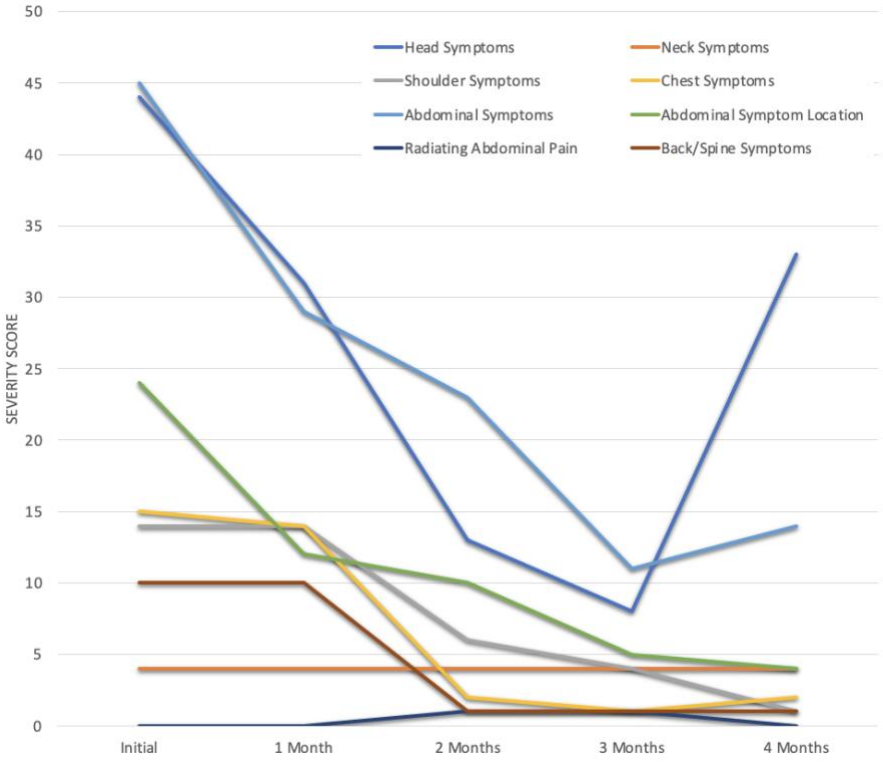

Figure 4.4 Symptom subgroup response to TENS in case #2 throughout four months of treatment.
Initial scores reflect the self-reported score prior to TENS treatment, each month reflects self-reported score after the specified duration of treatment. Data indicates success of treatment of GI dysmotility symptoms (>20% improvement from initial scores) after 4 months of treatment for shoulder (93% improvement), chest (87% improvement), abdominal (74% improvement) and back/spine (90% improvement) symptom groups. Improvements seen in head symptoms first 3 months of treatment, however increased score reported in month 4.

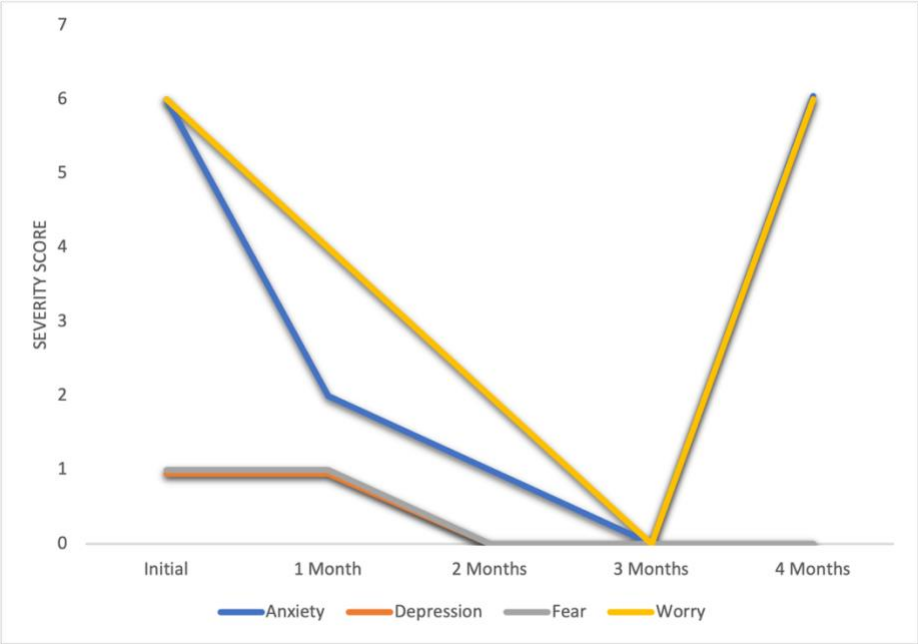

Figure 4.5 Head symptom response to TENS in case #2 throughout four months of treatment.
Increased reports of anxiety (blue) and worry (yellow) during the fourth month of TENS treatment.

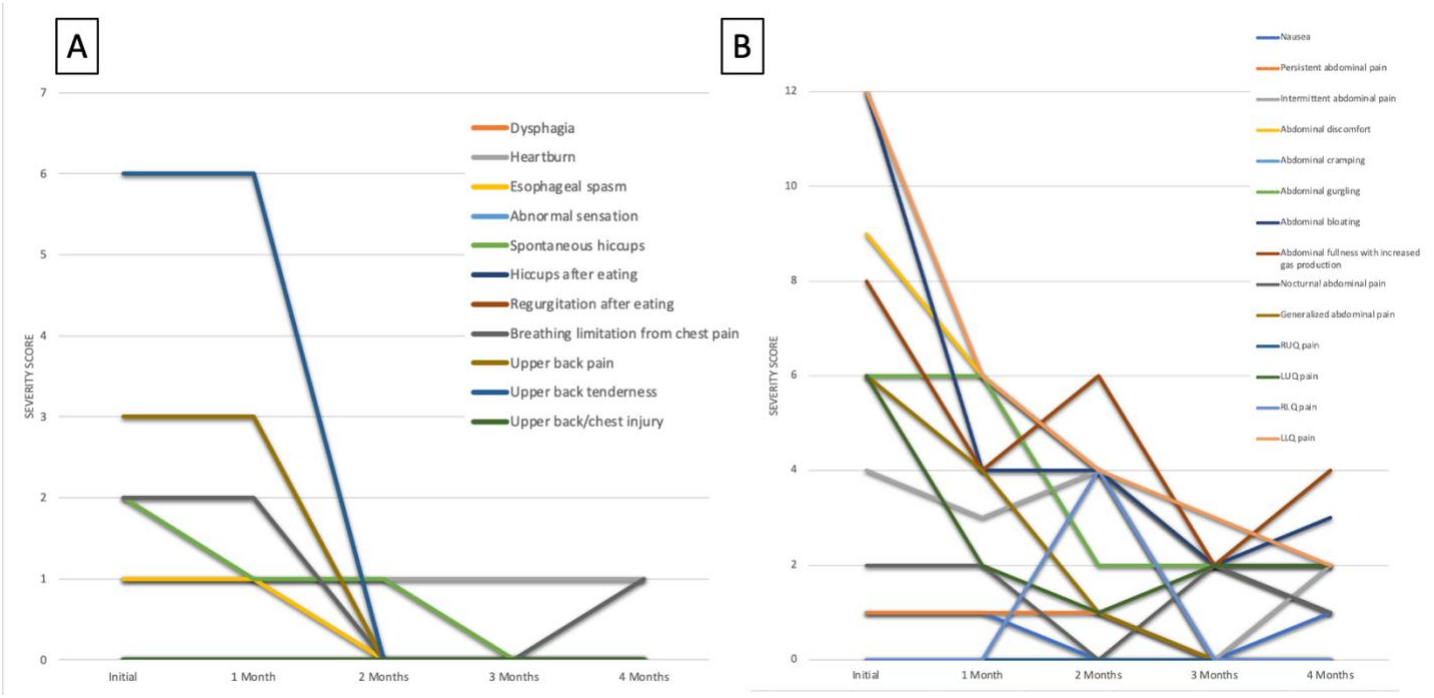

Figure 4.6 Symptom response to TENS in case #2 throughout four months of treatment.
Patient reports absence of esophageal spasm, breathing limitation due to chest/epigastric pain, upper back pain and upper back tenderness after 2 months of treatment. **B.** Score for abdominal symptoms prior to TENS treatment (initial) and reported scores after each month of treatment. Patient reports absence of persistent abdominal pain and postprandial abdominal pain in the generalized abdomen after 3 months of treatment, and improvements in intermittent abdominal pain, abdominal discomfort, abdominal gurgling, abdominal bloating, abdominal fullness with increased gas production, nocturnal abdominal pain, and postprandial abdominal pain in the LUQ and LLQ.

In a follow up 13 months after beginning TENS treatment, the patient reported to have completely discontinued all treatment since the 4-month treatment duration (9 months after discontinuation of the treatment) (Figure 4.7). The patient reported symptoms of constipation, abdominal gurgling, and pain in the left upper quadrant to remain at the same improved score as after 4 months of treatment (scored as *mild*) and reported abdominal pain in the generalized abdomen to remain absent. The patient did report increases in score for postprandial abdominal pain (reporting a score of 3 (mild) 4 months after treatment and reporting a score of 4 (moderate) 9 months post-TENS discontinuation) and LLQ pain (reporting a score of 2 (mild) 4 months after treatment and reporting a score of 4 (moderate) 9 months post-TENS discontinuation).

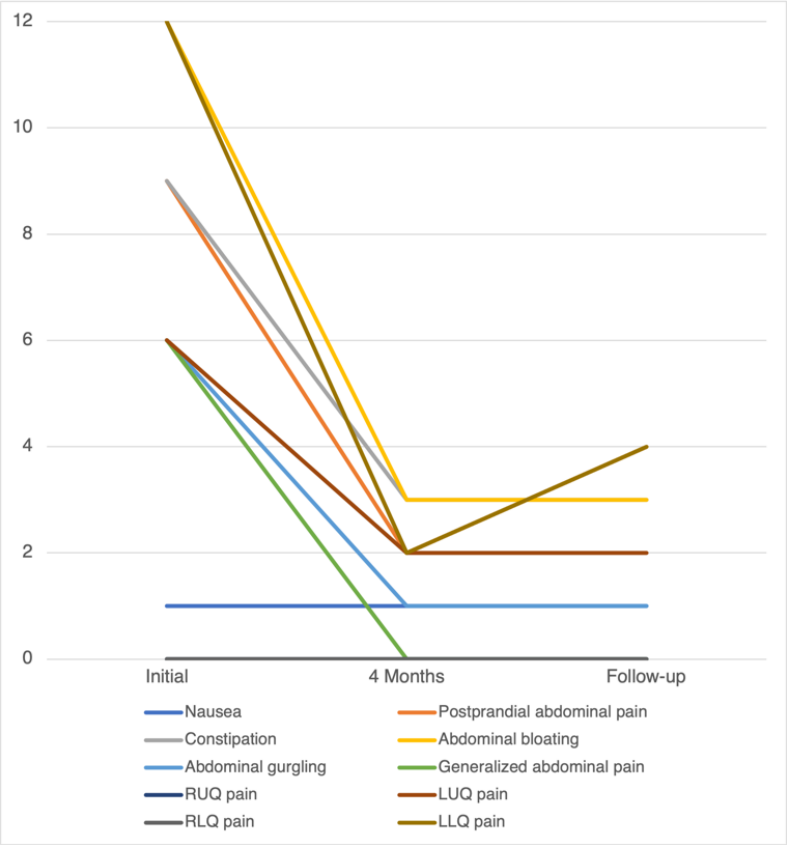

Figure 4.7 Symptom improvements lasting 9 months after discontinuation of TENS treatment for Case #2.
Graph indicates symptom scores reported prior to TENS treatment, after 4 months of treatment, and in a follow-up 9 months after discontinuation of the treatment. Symptom improvement shown to last beyond the discontinuation of the treatment.

4.4 Discussion

General

In the cases presented, we see patients with scoliosis of the thoracic spine, between T10-T12, both of which show severe GI symptoms and similar experiences of abdominal pain with unremarkable GI investigations. Both cases report severe postprandial abdominal pain, particularly in the epigastric to umbilical region and LLQ, sudden-onset constipation, very severe abdominal bloating, and nausea. These symptoms, particularly the experience of epigastric pain, constipation and nausea are consistent with the previously found symptoms indicative of scoliosis at T10-L2 (see Chapter 2).

TENS treatment was successful in treating sudden-onset constipation from *very severe* to *mild* or *absent* and abdominal bloating from *very severe* to *mild* in both patients. It also successfully treated abdominal pain reported by patients, with pain in the epigastric and generalized abdomen improving from *severe* to *mild* and *absent*, and pain in the LLQ of the abdomen improving from *severe* and *very severe* to *absent* and *mild*, respectively. Other symptoms associated with abdominal pain, such as abdominal cramping and

discomfort showed improvements. Additional symptoms of upper GI organs, such as postprandial hiccups and abdominal gurgling also showed improvements in response to TENS.

Some increases in symptom scores were reported by patients throughout their treatment. Case #1 reports some increases in mouth/throat and abdominal symptoms after one month of treatment, while case #2 reports some increases in abdominal symptoms after four months of treatment. It is important to consider various factors that may have impact on GI symptoms. Both patients reported increases in symptoms surrounding mental health, such as anxiety, fear and worry at the time of the corresponding month of increases in GI symptoms. There is a known positive correlation between anxiety and stress and sympathetic activity (Hoehn-Saric & McLeod, 1988), as well as anxiety and stress and GI symptoms (Lomax, Sharkey, & Furness, 2010), therefore these increases in mental health/head and GI symptoms may be related, however directionality of this relationship is not confirmed.

Measurement of autonomic nervous system function was only completed in Case #2 due to the COVID-19 pandemic. Autonomic testing in Case #2 showed sympathetic dominance at baseline and high sympathetic reactivity, while parasympathetic reactivity was exaggeratedly reduced during standing. High sympathetic tone and reactivity suggests that GI dysmotility and symptoms is likely due to sympathetic overload, hence, pathology likely involves thoracolumbar pathology-induced neuropathy leading to symptoms of GI dysmotility.

Both patients reported symptom improvements in response to TENS to last at least 9 months beyond the discontinuation of treatment. Only symptoms reported to increase again after discontinuation of treatment involve experiences of postprandial abdominal pain, and still indicate improvement from the symptom score pre-TENS. Case #1 reported increases in RLQ pain, which pre-TENS was reported as severe, after 3 months of TENS was reported as mild (score of 1) and 10 months post-discontinuation was reported as mild (score of 2). Case #2 reported increases in postprandial pain and LLQ pain, which pre-TENS were both reported as *very severe*, after 4 months of treatment were reported as *mild* (score of 2) and 9-months post-discontinuation was reported as *moderate* (score of 4). Other dominant symptoms were reported at the same scores as immediately after treatment. While increases are seen in some pain symptoms, reports of symptoms are significantly improved from those experienced prior to treatment, which were each reported as *severe* or *very severe*, indicating that symptom improvement in response to TENS remained at least 9 months post-discontinuation. These findings are consistent with findings of other studies involving prolonged effects of TENS beyond treatment time (Leong et al., 2011) (Hutson et al., 2015). These findings are also consistent with hypotheses of the mechanism of neuromodulation involving reactivation of neural circuitries in an allostatic state due to spinal pathology.

Underlying Mechanisms and Pathophysiology

Thoracolumbar spinal nerve pathology may cause extrinsic nerve innervation-related GI dysmotility symptoms, particularly severe abdominal pain. Each of the cases discussed have diagnostic imaging confirming scoliosis at the thoracolumbar region of the spine, with the potential to induce neuropathy. Such spinal conditions may affect visceral communication at the thoracic spinal level for the interpretation for nociceptive impulses from the periphery, resulting in experienced abdominal pain, and may also affect sympathetic innervation from the thoracic spine to the viscera, resulting in inhibition of GI motility and corresponding symptoms. Electrical stimulation of afferent and somatic fibres of the DRG of the thoracolumbar spine via TENS may affect the transmission of sensory pain signals from the periphery to the CNS (Deer et al., 2019), triggering different pathways and responses within spinal circuits (Ikeda, Asai, & Murase, 2000) (Chapman, Yousef, Foster, D Stanton-Hicks, & van Helmond, 2021). The extrinsic primary afferent neurons stimulated in the DRG have also been linked to the influence of myenteric neuron activity and smooth muscle contraction, linking pain and gastrointestinal motility via a sensory-parasympathetic spinal reflex (Smith-Edwards et al., 2019). Hence, spinal nerve neuropathy inducing the dysregulation of autonomic spinal pathways may be the pathology of both abdominal pain and GI dysmotility seen in these two cases. The stimulation of this spinal reflex circuitry provides an explanation as to how TENS shows improvements in both abdominal pain and GI dysmotility of patients, and long term effects support the hypothesis of neuromodulation stimulating autonomic spinal pathways back to a homeostatic state.

Conclusion

The two cases reported here suggests that symptoms of complex GI dysmotility, as well as symptom improvements seen in response to TENS treatment, supports the pathophysiological idea of spinal nerve pathology-related pain and dysmotility due to thoracolumbar (T10-L2) scoliosis in these two patients. Spinal nerve pathology may involve over-excitation of the sympathetic nervous system that inhibits colonic motility. The sympathetic overload in the allostatic state of chronic constipation may be enhanced by symptoms of stress and anxiety. Symptom improvements in response to TENS treatment may be due to reactivation of neural circuitries that are in allostasis due to patient spinal condition, as supported through symptom improvements lasting 9-10 months beyond the discontinuation of TENS treatment. The long-term benefits beyond discontinuation of TENS treatment needs to be further investigated in patients with complex dysmotility of upper GI organs and severe abdominal pain.

5 Evaluation of autonomic functioning in children with autism spectrum disorder

5.1 Introduction

As an autism support associate, I have been interested in the causes of autism and my current interest in autonomic nervous system dysfunctions, brought these topics together. After a scanning of the literature we felt the need to write a critical review. Much of the existing autonomic and HRV literature on autism has come to the conclusion that autonomic dysfunction is underlying autism, specifically hyperactive sympathetic activity and stunted parasympathetic activity, based on Porges' polyvagal theory. Given the high prevalence of GI motility disorders in children with autism, this review aims to look at the role of the autonomic nervous system in relation to both their autism diagnosis and their GI dysmotility. This review has allowed me to further understand the role of the autonomic nervous system in human conditions and the use of HRV analysis to best measure and analyze autonomic function.

5.2 Autism review

Below is the complete manuscript on autonomic functioning in children with ASD:

Autism spectrum disorder in children is not associated with abnormal autonomic nervous system function, hypothesis and theory.
https://doi.org/10.3389/fpsyt.2022.830234

ABSTRACT

The quest to understand the pathophysiology of autism spectrum disorder (ASD) has led to extensive literature that purports to provide evidence for autonomic dysfunction based on heart rate and heart rate variability (HRV), in particular respiratory sinus arrhythmia (RSA), a measure of parasympathetic functioning. Many studies conclude that autism is associated with vagal withdrawal and sympathetic hyperactivation based on HRV and electrodermal analyses. We will argue that a critical analysis of the data leads to the hypothesis that autonomic nervous system dysfunction is not a dominant feature of autism. Most children with ASD have normal parasympathetic baseline values and normal autonomic responses to social stimuli. The existing HRV and electrodermal data cannot lead to the conclusion of an over-excitation of the sympathetic nervous system. A small subgroup of ASD children in experimental settings has relatively low RSA values

and relatively high heart rates. The data suggest that this is likely associated with a relatively high level of anxiety during study conditions, associated with co-morbidities such as constipation, or due to the use of psychoactive medication. Many studies interpret their data to conform with the preferred hypothesis of autonomic dysfunction as a trait of autism, related to the polyvagal theory, but the HRV evidence is to the contrary. HRV analysis may identify children with ASD having autonomic dysfunction due to co-morbidities.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects social communication and social interaction. Heterogeneity of the condition results in a broad spectrum of presentations through symptoms and levels of functioning. ASD is often characterized by restrictive and repetitive patterns of behaviour (Szatmari, 2003) (American Association of Psychiatrists, 2021) and atypical social interactions (e.g., non-verbal behaviours, eye-gaze, facial expressions) (Lord, Rutter, & Le Couteur, 1994). Porges (Porges et al., 2013) proposed the idea that children with ASD are unable to display appropriate psychophysiological flexibility in response to stimuli due to autonomic inflexibility and chronic sympathetic activation. Individuals with ASD are described as in a chronic state of hyperarousal (Hutt, Hutt, Lee, & Ounsted, 1964). The polyvagal theory proposes that a functional 'vagal brake,' or spontaneous engagement and disengagement of the myelinated vagus based on environmental risk, is associated with behavioural flexibility and lowered vulnerability to stress (Porges, 2007) (Porges et al., 2013). It is suggested that children with ASD do not execute this vagal brake, therefore, they do not show autonomic flexibility to stimuli. The polyvagal theory indicates that this is due to dysfunction of the neuroception of a threat, leading to chronic vagal withdrawal and decreases in parasympathetic activity, specifically to unfamiliar social stimuli (Patriquin, Hartwig, Friedman, Porges, & Scarpa, 2019).

The measurement of respiratory sinus arrhythmia (RSA), a parasympathetic parameter of heart rate variability, is integral to the polyvagal theory, no doubt the reason why many studies on autonomic functioning in ASD often exclusively measure RSA. RSA is proposed as a portal, allowing accurate measurement of the dynamic influence of myelinated vagal efferent pathways onto the sino-atrial node; specifically, the communication between the nucleus ambiguous and the heart. The nucleus ambiguous is also critical for esophageal function and facial expressions associated with emotion (Porges, 1995). Although there are several mechanisms to modulate heart rate, only the myelinated vagal efferent pathways from the nucleus ambiguous via nicotinic preganglionic receptors on the sino-atrial node are proposed to be capable of the rapid, instantaneous changes that characterize RSA (Porges, 2007). Efferent projections from

the nucleus ambiguous are involved with processes associated with feeding and breathing, facial movements to express emotion, and to communicate internal states in a social context; RSA is proposed to measure this neuronal traffic (Porges, 1995).

Our objective was to evaluate the literature that *measured* features of the autonomic nervous system such as heart rate variability and electrodermal activity to evaluate the evidence of autonomic dysfunction in ASD.

Assessing autonomic dysfunction in ASD via heart rate and heart rate variability

Heart rate can react momentarily to changes in nervous input from the autonomic nervous system, and this property establishes heart rate variability (HRV) as a mirror of autonomic activity (Shaffer & Ginsberg, 2017) (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012) (Baevsky & Chernikova, 2017). HRV has been widely used to evaluate autonomic functioning, not only pertaining to cardiac function but to many other physiological and psychological aspects of body functioning (Berntson et al., 1997) (Ernst, 2017) (Shaffer & Ginsberg, 2017). HRV does not reflect exclusively cardiac control systems. For example, the parasympathetic regulation of breathing influences blood pressure and the subsequent activation of baroreceptors influences heart rate variability (Piepoli et al., 1997) (Grossman & Taylor, 2007). Hence, the autonomic regulation of breathing is seen in HRV. It is important to realize that the different HRV parameters for sympathetic or parasympathetic activity will not reflect all autonomic activity occurring throughout the body. Organs have distinct sympathetic and parasympathetic neuronal circuitries and activities that may or may not directly or indirectly influence HRV. Although there are many potential HRV parameters that can be evaluated, most autism studies employ heart rate and RSA (Sheinkopf, Neal-Beevers, Levine, Miller-Loncar, & Lester, 2013). Although the sympathetic nervous system is considered relevant to ASD and the polyvagal theory, it is usually not assessed, and if assessed, electrodermal activity is the dominant technique used.

General conclusions found in the literature based on heart rate and HRV analysis

All studies that use HRV as a measure of autonomic functioning in ASD link their findings to the polyvagal theory, but few provide actual raw data on HRV parameters which was also noted in a review by Benevides and Lane (Benevides & Lane, 2015). High baseline RSA is thought to be associated with adaptive social functioning (Diamond, Hicks, & Otter-Henderson, 2011), while low baseline RSA is believed to be associated with stress (Pico-Alfonso et al., 2007) and emotional dysregulation (Guy, Souders, Bradstreet, DeLussey, & Herrington, 2014). In socially safe contexts, heart rate is thought to decrease due to vagal activity from the nucleus ambiguous acting on the heart and promoting appropriate social behaviour (Porges, 2007). Studies evaluating ANS

functioning in ASD suggest chronic sympathetic activation and vagal withdrawal in autism due to findings of lower RSA and higher heart rate at baseline and in response to stimuli, compared to controls (Edmiston, Jones, & Corbett, 2016) (Guy et al., 2014) (Van Hecke et al., 2009). When studies report lower RSA and higher heart rate averages in both adults and children with ASD compared to a control group, the conclusion is that individuals with ASD exhibit chronic mobilization and impairment of the soothed autonomic state (Patriquin et al., 2019) (Guy et al., 2014). It is suggested that children with ASD have inaccurate nervous system perception when assessing risk, preventing the inhibition of limbic structures for immobilization and resulting in chronic vagal withdrawal (Patriquin et al., 2019) (Van Hecke et al., 2009). We will argue that the perceived attractiveness of the polyvagal theory leads many authors to conclude that their HRV results are consistent with the theory, despite their data indicating otherwise.

Critical analysis of HRV parameter assessments.

Do children with ASD have an abnormal baseline RSA?

Despite numerous assertions in the literature to the contrary, the absolute values of baseline RSA of children with ASD are almost all within the normal range. The wide range of normal RSA values in children was documented by Harteveld et al., who reported on 4822 children aged 0.5-20 years (Harteveld et al., 2021). Harteveld et al. (Harteveld et al., 2021) used the peak-valley method, measuring RSA by subtracting the shortest inter-beat interval during inhalation from the longest inter-beat interval during exhalation, and found that for 328 children aged 13-15, the RSA ranged from 18.7 – 186.7 ms (2.5 - 97.5 percentile), hence a very wide normal range. In a personal communication, Harteveld calculated the range of RSA values (2.5 – 97.5 percentile) in 99 typically developing children, age 4-18, to be 4.5 - 8.8 ln(ms^2) (Table 5.1). Dollar et al. studied 270 children and followed them from 2-15 years. For ~ 200 children, the RSA at 10 and 15 years ranged from 5.5 -7.8 ln(ms^2) (Figure 5.1) (Dollar et al., 2020).

When the values of heart rate or RSA of a cohort of children with ASD are compared to neurotypical children, the average values can show statistically significant differences. However, almost all children with ASD in those studies have values within the normal range, *even when compared to the control group of that study* (Figure 5.1). If most children with ASD have values within the range of control values, one cannot make the general statement that children with ASD have abnormal RSA values, implying autonomic dysfunction (Huizinga, Mathewson, & Yuan…, 2018). Suppose some children with ASD fall outside of chosen confidence levels, say outside the 95% confidence interval. In that case, a subgroup may be the reason for the significant difference from the control group, and the existence of a subgroup may be highly clinically significant. It is

well known that ASD has heterogeneous pathophysiology. Once a statistically significant difference is found, the reason for it should be established. Then the question ought to be whether the difference is physiologically and clinically significant or relevant. Hence, the statement that "a group of children with ASD have a statistically significant lower RSA baseline compared to a group of normally developing children" is not equivalent to the statement that "children with ASD have a low RSA baseline" and most certainly not that "children with ASD have autonomic dysfunction."

Kushki et al. (Kushki, Brian, Dupuis, & Anagnostou, 2014) and Muscatello et al. (Muscatello, Vandekar, & Corbett, 2021) did not observe baseline RSA differences. Corbett et al. reported that children with ASD did not show poor autonomic regulation during social interaction with novel peers, based on similar RSA values (Corbett, Muscatello, & Baldinger, 2019). Vaughan van Hecke et al. (Van Hecke et al., 2009) reported baseline RSA to be significantly lower in an ASD group compared to typically developing controls. While statistically significant, the RSA values in the group of children with ASD fall within the normal range of control values (Harteveld et al., 2021), and most values also fall within the experimental control group values (Figure 5.1); hence their conclusion that "ASD patients have a lower baseline RSA" is not correct. The only valid conclusion is that a small subgroup of patients with RSA values falls outside the control group's confidence levels (or average ± one standard deviation range).

Edmiston et al. (Edmiston et al., 2016) recorded baseline RSA values in ASD children, finding that the average value was different from that in controls (Figure 5.1) and concluded that children with ASD have "reduced physiological self-regulation." This conclusion must be rejected since the average RSA value of children with ASD, between 12- and 18 yrs, was ~ 6.9 ln(ms^2) which is entirely normal. There are no data that show that an RSA of 6.9 ln(ms^2) constitutes autonomic dysfunction. Bal et al. (Bal et al., 2010), based on RSA baseline values, stated that children with autism have "lower overall vagal regulation of the heart"; this is not only incorrect, since the absolute baseline values fall within the overall normal range, it is also misleading to suggest that something is wrong with regulation of cardiac function. Neuhaus correlated baseline RSA values with autism features, but the average baseline RSA of 6.9 ln(ms^2) in the children with autism cannot be interpreted as indicating autonomic dysfunction (Neuhaus, Bernier, & Beauchaine, 2016). Miller tried to relate baseline RSA values, which are mainly normal, with features of autism, but no linear relationships were found (Miller, Kahle, & Hastings, 2017) (Toichi & Kamio, 2003).

It is illustrative to point out that when positive findings are found, they are often judged to be unreliable, indicating the desire to find dysfunction. For example: "Adults with autism demonstrated significantly higher baseline HRV (using the root mean square of successive differences (RMSSD)) compared to control groups (Zahn, Rumsey, & Van Kammen, 1987) possibly suggesting effective interventions/supports to develop control over their physiological state or, alternatively, that higher RMSSD values may have been

inflated due to movement or heart rate and respiratory influences" (Patriquin et al., 2019). Zahn et al. concluded that none of the variables to index the construct of autonomic nervous system arousal was significantly different from controls (Zahn et al., 1987). When Smeekens et al. did not find any differences in autonomic or endocrine activity with social functioning in adults, it was thought to be due to lack of power (Smeekens, Didden, & Verhoeven, 2015), and a non-significant effect was worded as a "blunted increase."

Bricout (Bricout, Pace, Dumortier, Favre-Juvin, & Guinot, 2018) used a clinically prominent test for autonomic dysfunction and found that children with ASD did not have clinical signs of dysautonomia in response to the head-up tilt test. As reflected by RMSSD, their baseline parasympathetic tone was also not different from controls. In a case series of 6 patients with ASD who had symptoms of autonomic dysfunction: postural light-headedness, near syncope, constipation, diarrhea and early satiety, all had postural tachycardia, but no orthostatic hypotension (Goodman, 2016). The absence of orthostatic hypotension is interesting since it is a common feature of neurodegenerative disorders (Metzler, Duerr, Granata, & Krismer…, 2013).

Table 5.1 Control values in a cohort of healthy children from a study by Nederend et al. (Nederend et al., 2017) as shown in Harteveld et al. (Harteveld et al., 2021). Data was obtained through personal communication with Dr. L.M. Harteveld with permission.

Age (Y)	ln HF											
	Boys						Girls					
	N	Median	Percentile		Mean	SD	N	Median	Percentile		Mean	SD
			2.5th	97.5th					2.5th	97.5th		
1-3	8	5,01	4,68	6,42	5,42	,74	10	5,34	3,33	7,28	5,26	1,27
4-7	17	7,62	5,06	8,63	7,13	1,12	6	7,09	6,43	8,74	7,39	,94
8-10	8	7,70	5,53	8,63	7,54	1,06	12	7,07	4,45	8,84	6,73	1,44
11-12	9	7,16	5,94	9,01	7,35	1,05	8	7,50	5,72	8,01	7,38	,79
13-15	11	7,03	5,02	7,69	6,90	,78	13	7,22	5,82	9,31	7,32	1,06
16-18	8	6,54	5,45	7,19	6,61	,58	7	6,02	4,74	8,33	6,37	1,23

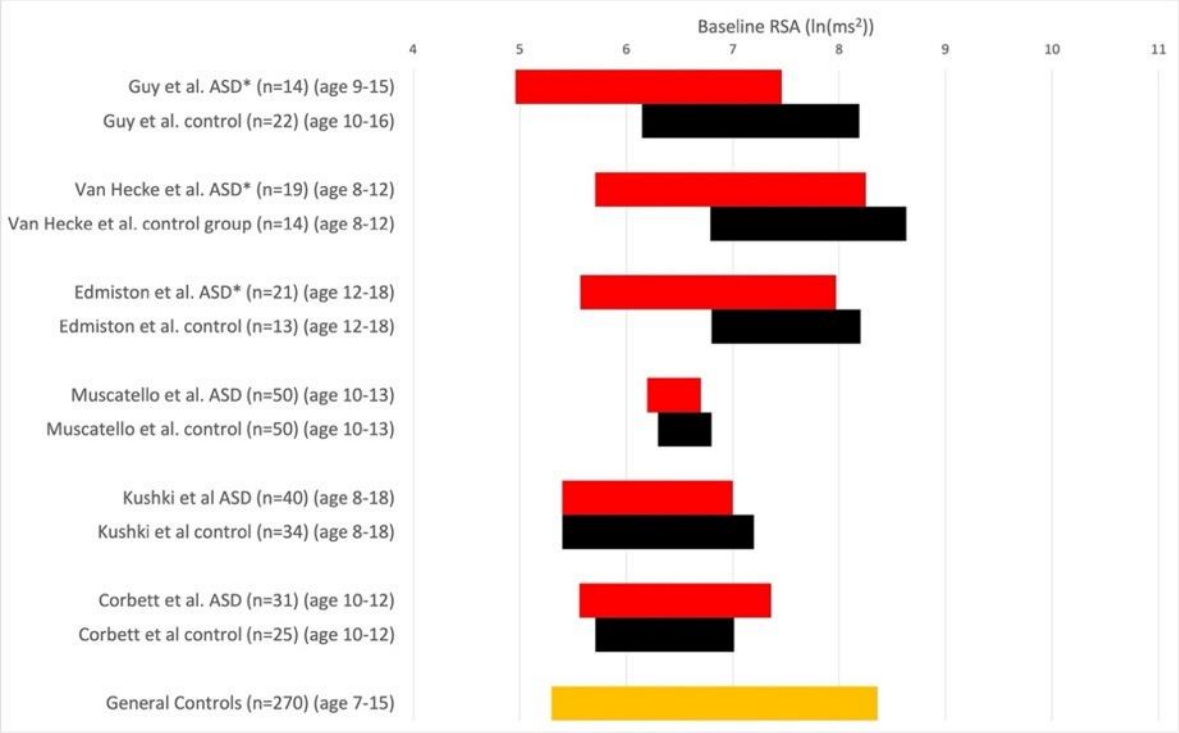

Figure 5.1 RSA is expressed in comparative studies with an ASD group (red) and typically developing children (control, black).
RSA ± 1SD; * = P<0.05 compared to in-study controls. Others: no significant difference. Note that comparisons cannot be absolute because of differences in measuring RSA. Muscatello et al. (Muscatello et al., 2021) and Corbett et al. (Corbett et al., 2019) used ln(HF power) with the HF range of 0.12 – 0.40Hz, Kuski et al. (Kushki et al., 2014) used 0.24-1.04 Hz. Edmiston et al. (Edmiston et al., 2016)used 0.15-0.40 Hz. Guy et al. (Guy et al., 2014) report that the amplitude of RSA was calculated as the natural logarithm of the extracted variance for each successive 30-second epoch within 12-1Hz (probably 0.12 – 1Hz). Vaughan van Hecke (Van Hecke et al., 2009) chose the natural logarithm of the variance of the band-pass series from HF, 0.12 – 1 Hz. At the bottom, the orange control values are derived from a study that examined RSA over time in 270 children (Dollar et al., 2020); we used a range based on their average values ± 1 SD from ages 7-15, obtaining a normal range of 5.3 – 8.4 ln(ms^2).

Do children with ASD have an abnormal RSA in response to stimuli?

Assessment of RSA reactivity to stimuli is probably the most relevant experimental condition to be studied concerning potential autonomic dysfunction related to ASD in the context of HRV. This has been assessed in two ways, analysis of differences in absolute values of RSA during the experimental conditions (Figure 5.3) and reactivity, the difference between baseline and experimental condition. HRV in response to a stressful mental load has consistently shown to decrease HRV, including a decrease in RSA (Toichi & Kamio, 2003). Hence a decrease would show autonomic flexibility.

Figure 5.2 shows data from an important study by Kushki et al. (Kushki et al., 2014). The data pertaining to baseline RSA and RSA reactivity and baseline heart rate and heart rate reactivity to various stimuli leave us with only one logical conclusion, that ASD children have normal autonomic functioning. Tasks are accompanied by an increase

in heart rate and a decrease in RSA, similar to controls, consistent with the author's results statement: "After controlling for age, sex and full-scale IQ, the performance of children in the ASD group was not significantly different from that of the typically developing control group on any of the five tasks in this study." Yet, the authors state: "In the absence of such differences, ANS atypicalities may suggest compensatory mechanisms applied by the ASD group" (Kushki et al., 2014). A simpler and likely better explanation is that the ASD children did not show any clinically significant autonomic dysfunction. The desire to find differences can be deduced from this statement: "Our results suggest atypical cardiac findings..... in particular, while not statistically significant, we found that the ASD group had an elevated heart rate during the experimental session" (Kushki et al., 2014). Hence, even though there was no statistical difference between children with autism and the control group, this non-difference is suggested to be an "atypical cardiac finding." The conclusion of the authors that "ASD children show selective atypical reactivity" does not appear to have clinical relevance.

Guy et al. (Guy et al., 2014) conducted a study investigating the RSA response to cognitive and social stimuli in children with ASD compared to age- and IQ-matched typically developing controls. The study reports that ASD is associated with abnormal HRV (lower RSA) across all tasks, corroborating the polyvagal theory and concluding that low RSA in autism is due to less parasympathetic activity and vagal withdrawal. While differences in reported RSA values are statistically significant, the absolute values of RSA in ASD groups (Figure 5.3) (6.29 $\ln(ms^2)$ during a cognitive task; 6.61 $\ln(ms^2)$ during a social task) fall categorically within the normal range of typically developing controls. Hence, the conclusion of abnormal RSA in children with ASD is not supported. The discussion states that all findings could be related to anxiety, and yet it is stated that the data support the use of HRV as a biomarker for ASD (Guy et al., 2014).

Muscatello et al. (Muscatello et al., 2021) exposed participants to a social interaction protocol, the Trier Social Stress Test-Friendly (TSST-F). The data show that "ASD and typically developing youth did not differ in mean RSA or RSA responsivity during the TSST-F paradigm when controlling for age." Instead of giving the study the title that no evidence of autonomic dysfunction was found, the title became "Evidence for decreased parasympathetic response to a novel peer interaction in older children with autism spectrum disorder." The term "decreased parasympathetic" does not appear in the study itself; instead, the term "blunted" is used; however, no statistical differences were found.

Toichi and Kamio (Toichi & Kamio, 2003) studied high functioning young adults with ASD to avoid confounding factors such as the inability to sit still. They did not find any differences with a control group related to heart rate, sympathetic activity or resting parasympathetic activity. The parasympathetic activity (measured based on the Lorenz plot) decreased in 18/20 controls with no change in 2/20. In contrast, the ASD group showed a decrease in 10/20, 3/20 did not show a response and 7/10 showed an increase,

although this increase was not repeated when other types of mental activity were examined. The authors suggest several explanations for an increase in parasympathetic activity. Some persons with ASD might find mental tasks relaxing, or it may be related to the functioning of the amygdala (Toichi & Kamio, 2003). Interestingly, Muscatello et al. (Muscatello et al., 2021) studied the effect of social interactions to promote a relaxing environment. Indeed, the RSA increased, but did so similarly in the control and the ASD group. The increase in RSA in both control and ASD in the study by Guy et al. related to a social task that involved a positive social engagement with an adult clinician (Guy et al., 2014).

Edmiston et al. concluded that social problems in ASD may be linked to the RSA response to social stress; however, the RSA response to the stress was the same as in controls, a reduction of ~ 1 unit ln(ms^2) (Edmiston et al., 2016). The absolute values of RSA during social judgment were statistically different from the control group. Still, the response was the same, and the absolute values were also normal and strongly overlapping.

Watson et al. (Watson, Roberts, Baranek, Mandulak, & Dalton, 2012) showed that RSA findings for children with ASD who had no or limited expressive language showed no significant difference from control groups in response to both non-social and social stimuli, concluding that their findings do not show that ASD participants have an underactive parasympathetic nervous system or disproportional arousal when attending to social versus non-social stimuli.

Bazelmans et al. (Bazelmans, Jones, & Ghods…, 2019) showed that watching naturalistic videos did not show differences in heart rate or RSA between ASD and typically developing children and concluded that HRV did not produce biomarkers for ASD. In autistic adults, no differences in autonomic or endocrine parameters were found in response to a social interaction with an unfamiliar person, compared to a control group (Smeekens et al., 2015).

A recent meta-analysis incorporating most studies reported here states that their analysis supports low HRV as a potential biomarker of ASD without critically evaluating the studies (Cheng, Huang, & Huang, 2020). Their bias was formulated in the introduction: “ASD feature stereotyped thought, behaviour and problems of social interaction, therefore the connection between individuals with ASD and low HRV should be intuitive.” The study concludes that HRV does not differentiate ASD from other psychiatric disorders and suggests that results and conclusions should be viewed cautiously because co-morbidities might affect HRV, and this was not accounted for (Cheng et al., 2020). Hence, the conclusion that HRV is a biomarker for ASD is not warranted.

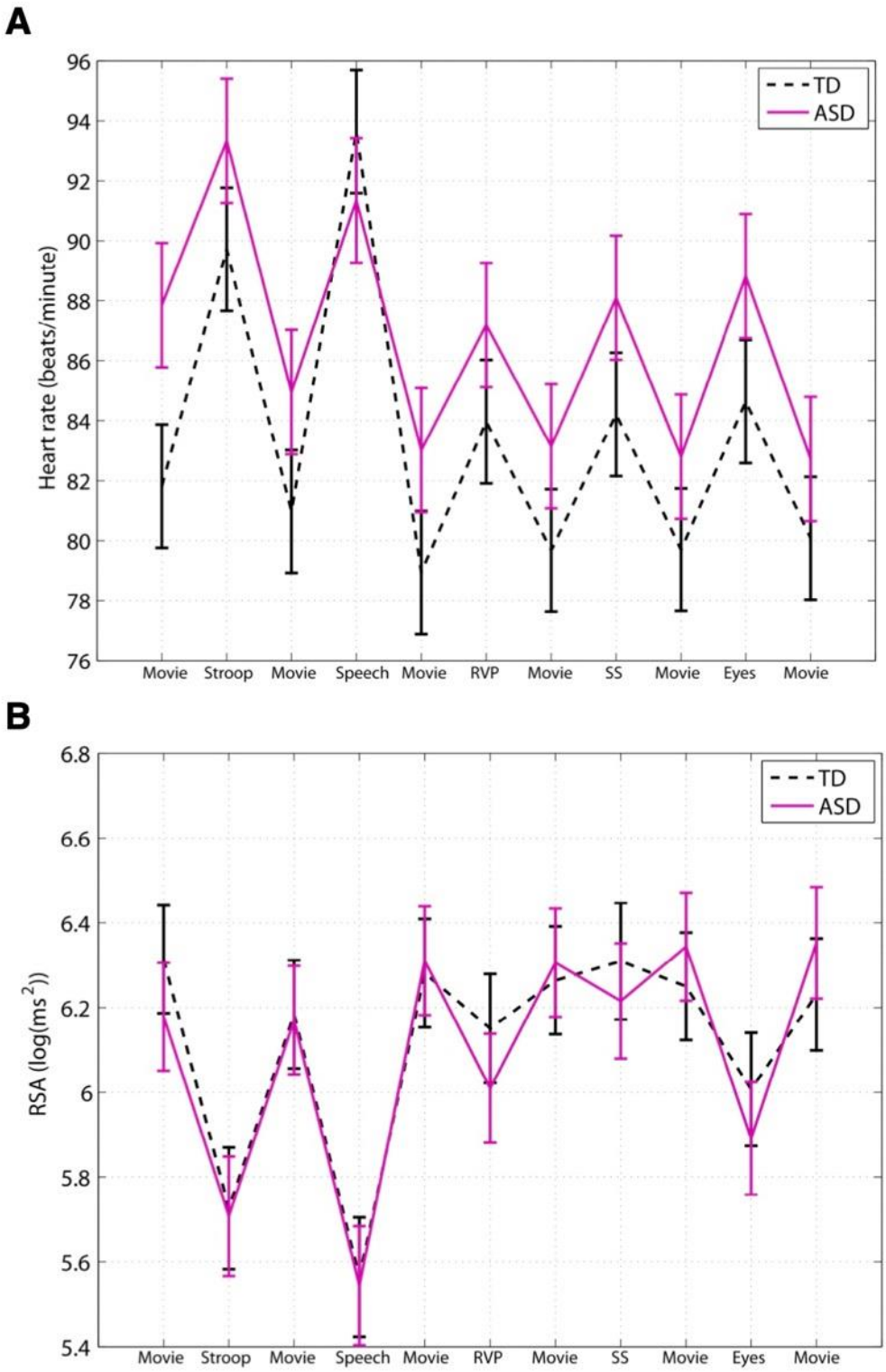

Figure 5.2 Children with ASD have a normal baseline HRV parameter and a normal autonomic response to social stimuli.
This figure is taken from a study by Kushki et al. (Kushki et al., 2014); they studied autonomic regulation in children with autism while performing tasks that elicit anxiety, attention, response

inhibition and social cognition. Expressed are heart rate (A) and RSA (B). The authors conclude that children with ASD show overall autonomic hyperarousal and selective atypical reactivity to social tasks. **A**: The average baseline heart rate of the children with ASD was 88 bpm, which is not indicative of cardiac dysfunction nor an overactive sympathetic nervous system; it cannot be interpreted to show that children with ASD show hyperarousal. **B**: There were no statistical differences in baseline RSA nor general group differences. Evaluating each task, there were no differences in RSA reactivity in the Stroop, public speaking or rapid visual information processing tasks. The reading the mind in the eyes task also did not show a significant difference except when the medication group was excluded. However, both the control group and the ASD children showed a normal strong decrease in RSA, and there is no evidence that this difference is clinically significant. (TD), n=34, and ASD children, n=40. “Movie”: considered resting baseline; “Stroop”: eliciting a stress reaction; “Speech” public speaking considered anxiety eliciting; “RVP”: rapid visual information processing, eliciting sustained attention; “SS”: stop-signal task, testing response inhibition; “Eyes”: reading the mind in the eyes, testing social cognition. The figure labels RSA to be log(ms^2) however the values indicate that RSA is likely ln(ms^2).

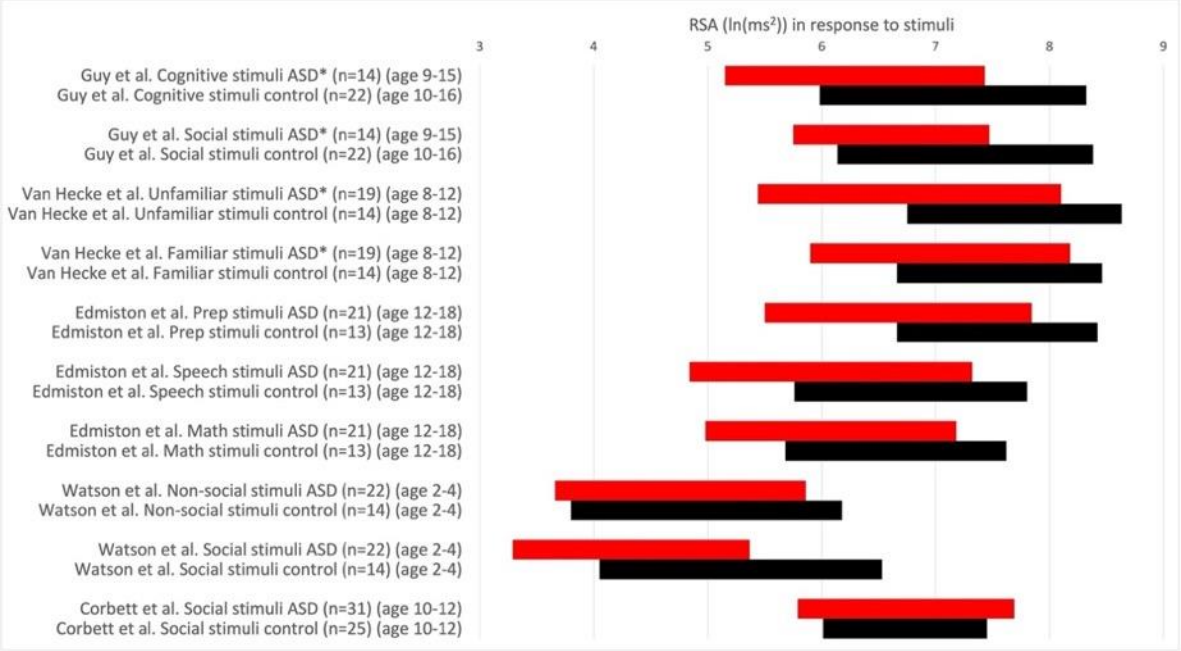

Figure 5.3 RSA values in response to stimuli
RSA values are expressed comparing the response to stimuli in children with ASD (red) and a control group (black). RSA ± 1SD. * = P<0.05. Others: no significant difference. RSA is expressed in ln(ms^2).

Do children with ASD have an increased abnormal basal heart rate?

In many studies, the average baseline heart rate value in a cohort of children with ASD is higher compared to the control group. However, most ASD children have a heart rate that falls not only into the general normal heart rate range (Ostchega, Porter, Hughes, Dillon, & Nwankwo, 2011), it also falls within the range of normal values of the controls in the study, indicating that most ASD children have a normal heart rate from any perspective. Throughout the ASD literature, all heart rates are obtained in an experimental condition. Hence, if some children with ASD feel a higher level of anxiety in

an experimental setting (Russell & Sofronoff, 2005), the average heart rate of children with ASD in that group would likely be higher than the average heart rate of controls. The experimental conditions of studies are rarely accounted for. Yet, they are a valid factor that may account for higher averages of heart rate often seen in ASD groups, despite most individual ASD participants showing normal heart rate values. When a group of ASD children is compared to a group of typically developing controls, and the a*verage* heart rate value is higher in the ASD group, but most children in the ASD group have a normal heart rate, one can conclude that "the autism group has a significantly increased heart rate compared to the control group," but one cannot conclude that "children with autism have an increased heart rate" and one can definitely not make the general statement that "children with ASD show sympathetic hyperarousal."

Bal et al. (Bal et al., 2010) conclude that children with ASD have significantly faster baseline heart rate than typically developing controls. While the ASD group's mean heart rate value was significantly higher than the typically developing control group, the heart rate of the ASD group was still within the normal range of the age demographics (Ostchega et al., 2011) as shown in Figure 5.4. The study concludes that ASD children had "lower overall vagal regulation of heart rate" and "hyperactive sympathetic activity" (Bal et al., 2010). These conclusions cannot be supported as the children with ASD have a clinically normal heart rate. A simple statement about sympathetic activity should also not be made based on heart rate alone, without measuring sympathetic activity directly. Kushki et al. (Kushki et al., 2014) concluded that children with ASD have "overall autonomic hyperarousal" based on a "marginally elevated basal heart rate." The average baseline heart rate of the children with ASD was 88 bpm, which is not indicative of cardiac dysfunction nor an overactive sympathetic nervous system (see Figure 5.4).

Bujnakova et al. (Bujnakova et al., 2016) concluded that a higher heart rate at baseline in children with ASD compared to the age-matched control group indicated tachycardia; however, an average heart rate of 83 bpm in 7–15-year-old children does not indicate tachycardia. The heart rate values in this study are within the normal range of its age and gender demographics (Ostchega et al., 2011); hence it is unreasonable to conclude autonomic deficits based on these baseline heart rate data. The authors do mention the questionability of their findings related to comorbid psychiatric symptoms.

When children with ASD were grouped into those with known autonomic dysfunction (gastrointestinal motility problems or syncope, etc.) and those without, the heart rate and blood pressure were similar in controls and asymptomatics. They increased in symptomatics suggesting higher heart rate to be due to comorbidity and not autism per se (Ming, Julu, Brimacombe, Connor, & Daniels, 2005).

A group of 116 controls and 154 children with ASD showed an average heart rate of 90.1 and 95.2 bpm, respectively, which was significantly different; however, when only the 82 non-medicated ASD children were assessed, there was no difference with the control group (Daluwatte et al., 2013).

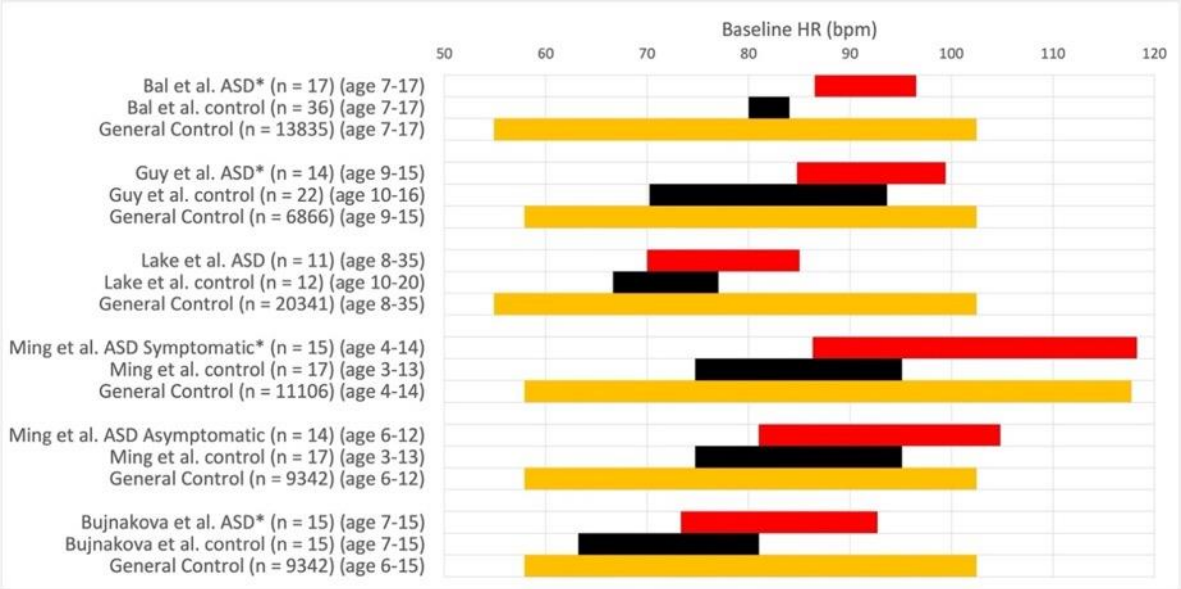

Figure 5.4 Heart rate values (HR ± 1SD) at baseline.
HR expressed in comparative studies with an ASD group (red) and a group with typically developing children (control, black) and normal HR values in a large of children taken from Ostchega et al. (orange) (Ostchega et al., 2011). * = P<0.05. Others: no significant difference.

Do children with ASD have an abnormal increase in heart rate in response to stimuli?

Many studies in the autism literature find a higher heart rate in ASD groups at baseline, which remains consistent throughout exposure to stimuli, but this does not constitute a higher heart rate response. Kushki et al. (Kushki et al., 2014) found no significant group differences for heart rate reactivity in the Stroop, Rapid Visual Information Processing, Stop Signal or Reading the Mind in the Eyes tasks (Figure 5.2). The authors report blunted heart rate reactivity to social anxiety tasks due to reduced responsivity to the public speaking task; however data pertaining to heart rate responsivity in each task suggest excellent autonomic reactivity (Figure 5.2). They conclude atypical heart rate reactivity to social tasks, despite the increase in heart rate seen in both the ASD and control groups for all stimuli, which suggests that no autonomic dysfunction is present in the ASD group. Sheinkopf et al. (Sheinkopf et al., 2013) found that the ASD and control groups did not differ in mean heart rate during all stimulus conditions. With “distal stranger” stimuli, both groups had a heart rate that remained approximately the same, whereas with “proximal stranger” stimuli, both groups had decreased heart rate with no differences shown among groups (Figure 5.5).

Neuhaus et al. (Neuhaus et al., 2016) found that, in contrast to their expectations, the children with ASD had a normal heart rate and RSA response to interactions with a novel partner, indicating typical autonomic reactivity (Figure 5.5).

Watson et al. (Watson et al., 2012) found that an ASD group had a faster heart rate than age-matched controls, but heart rate was not specific to stimulus type for non-social and social stimuli. They conclude that their data do not support an underactive parasympathetic system nor disproportionate arousal when attending social stimuli. No differences in RSA in response to stimuli were observed between the ASD group and controls (Figure 5.5).

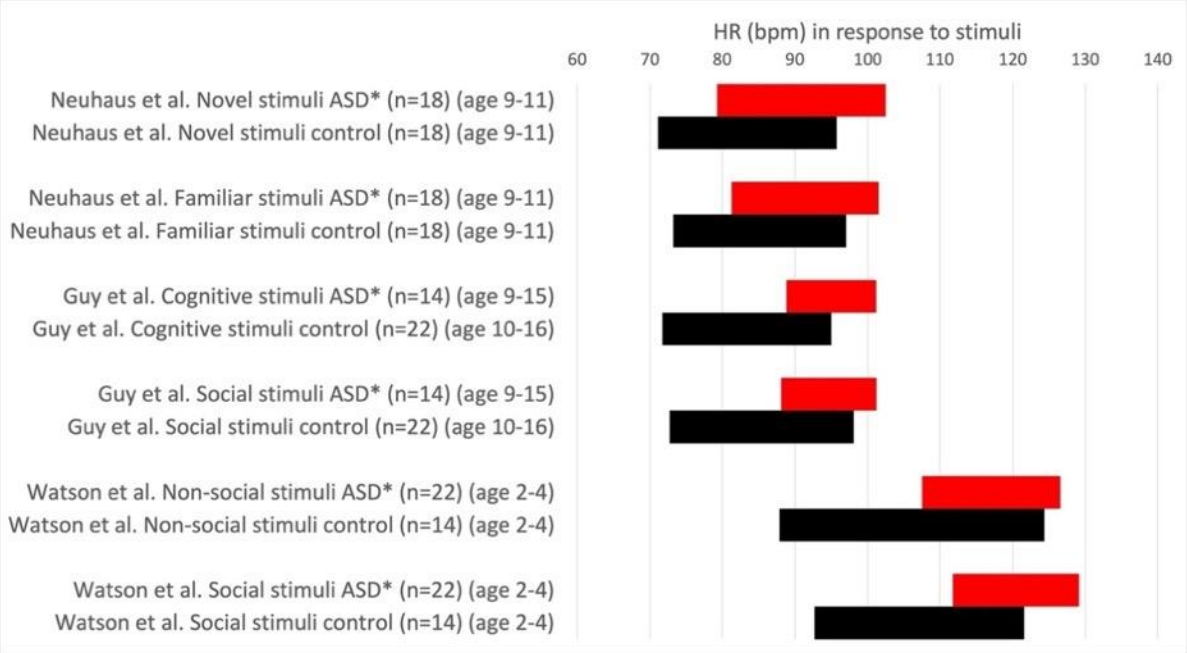

Figure 5.5 Heart rate values (HR ± 1SD) in response to stimuli.
HR is expressed in comparative studies with an ASD group (red) and typically developing children (control, black). * = P<0.05. Others: no significant difference.

Can potential parasympathetic autonomic dysfunction in ASD be assessed using the pupillary light reflex?

The pupillary light reflex expresses the constriction and subsequent dilation of the pupil in response to light as a result of the antagonistic actions of the iris sphincter and the dilator muscles (Hall & Chilcott, 2018). Latency and constriction are under parasympathetic control. Subsequent relaxation is due to sympathetic inhibition of parasympathetic neurons at the Edinger-Westphal nucleus as well as sympathetic contraction of the iris dilator muscle (Hall & Chilcott, 2018). Nyström et al. concluded that "infants at risk for autism have a hypersensitive pupillary light reflex," suggested to be due to cholinergic autonomic "disruptions"; however, most infants had latency and constriction amplitudes that fell within the range of the control values (Nyström, Gredebäck, Bölte, Falck-Ytter, & EASE, 2015). Daluwatte et al. showed that children with ASD, on average, have significantly longer latency and reduced pupil constriction amplitude in response to light compared to typically developing children; the difference in reflex parameters was

suggested to be due to parasympathetic dysfunction, but it was not accompanied by a significant difference in RMSSD values (Daluwatte et al., 2013). Fan et al. studied a group of children and young adults with ASD (Fan, Miles, Takahashi, & Yao, 2009). They showed that the pupillary light reflex features, in particular the reflex latency, could discriminate between the ASD group and a control group, particularly the reflex latency. Lower constriction velocities were found in children with ASD compared with the typically developing control group, but this was statistically significant only at a light-adapted reflex stimulus intensity of 872 cd/m^2 and not at different intensities; the ASD group exhibited significantly smaller relative constriction at a dark-adapted reflex stimulus intensity of 794 cd/m^2 but not at different intensities (Fan et al., 2009). There was no statistical difference in the reflex recovery velocity between the two groups (Fan et al., 2009).

Hence, children with autism have a robust pupillary light reflex. They may have a response that is not different from typically developing children, or they may have a response that is different in some features but not in other characteristics. The question is whether such a difference indicates pathophysiology, and if so, how this may correlate with autonomic functioning related to ASD traits or comorbidities.

Assessment of sympathetic activity.

The polyvagal theory predicts that children with autism would have a “hyper-responsive sympathetic system” (Bal et al., 2010) (Panju, Brian, Dupuis, Anagnostou, & Kushki, 2015). To support this theory, autistic children should have a high sympathetic tone and exaggerated sympathetic responses to stress-provoking stimuli. An often-cited study by Hirstein et al. (Hirstein, Iversen, & Ramachandran, 2001) makes strong statements about sympathetic autonomic dysfunction in children with autism, but it is dominated by discussion, with very few study data presented, and hence should be interpreted with caution. Hirstein et al. hypothesize that amygdala damage in children with autism causes disastrous brain malfunctions. They hypothesize that autistic children have chronic high sympathetic activity that they try to reduce by calming activities such as repetitive behaviours and that “autistic children use overt behaviour in order to control a malfunctioning autonomic nervous system,” but no data to support this are provided.

Most studies on sympathetic activity in children with ASD use electrodermal activity. Electrodermal activity is defined as the electrical conductivity between two electrodes on the skin over time; it provides an index of sympathetic nervous system activity since eccrine sweat glands are innervated by the sympathetic but not parasympathetic branch of the autonomic nervous system (Boucsein et al., 2012). Although the study of electrodermal activity appears to be a logical non-invasive choice, there is no direct evidence that whatever brain sympathetic activity we are interested in

is faithfully captured by electrodermal activity, but it might. The expectation is that during mental exercises, the sympathetic nervous system will be activated to respond to energy demand to increase blood glucose. If an exercise were accompanied by marked anxiety, this would further increase sympathetic activity.

Most studies using electrodermal activity do not support the theory of an overactive sympathetic system. Panju expected to find sympathetic hyperarousal and studied ASD children with high and low levels of anxiety; compared to a control group, ASD children with low levels of anxiety were not different from controls in baseline electrodermal activity nor in sympathetic responses to any stimulus (Panju et al., 2015). Contrary to their expectations, the baseline electrodermal activity in children with high anxiety levels was lower than controls. Levine et al. showed that in response to the Trier Social Stress Test, both ASD children and a control group showed a similar increase in sympathetic (electrodermal) activity (Levine et al., 2012). Toddlers with ASD displayed comparable electrodermal reactivity as typically developing peers in response to sensory stimuli in visual, auditory, tactile, and olfactory modalities as well as visual displays of repetitive movement (McCormick et al., 2014). Joseph et al. showed normal baseline values. In measuring face recognition accuracy by skin conductance response, almost all children with ASD fell into the normal range with a few outliers (Joseph, Ehrman, McNally, & Keehn, 2008). In an excellent study on assessing sympathetic activity in toddlers using skin conductance, where all the data were displayed in scatter plots (Vernetti et al., 2020), eliciting anger, frustration or joy evoked a similar increase in sympathetic activity in the ASD and control group. In response to a fear-inducing stimulus, the control group exhibited an *increase* while the ASD group exhibited a *decrease* in sympathetic activity, although the scatter plots show that most children with ASD and controls have a response that centers around 0. Hence a correct conclusion appears that some children with ASD have a *decreased* sympathetic response to fear stimuli. The authors did not find a statistically significant difference in baseline sympathetic values and no correlation between the degree of sympathetic responses and the severity of autism. They conclude that toddlers with ASD should not be labelled as “dysregulated” or “upregulated” (Vernetti et al., 2020). However, unfortunately, they chose a title to their study that suggests the opposite. Bujnakova et al. (Bujnakova et al., 2016) found lower values in children with ASD and suggested under-arousal, but discussed that this might reflect co-morbidities and not autism per se.

Muscatello et al. (Muscatello et al., 2021) studied the pre-ejection period, and no difference was found related to social tasks. However, the pre-ejection period is a measure of ventricular contractility and is not a good measure of general sympathetic functioning (Ali, Liu, Chen, & Huizinga, 2021). For example, the pre-ejection period does not change with postural change from supine to standing, whereas it is well known that sympathetic activity markedly increases (Ali et al., 2021).

Using the Poincaré plot, no sympathetic differences in resting conditions, not responses to a mental task, were found in adolescents with ASD compared to controls (Toichi & Kamio, 2003).

In summary, the overall conclusion must be that assessments of sympathetic activity in children with ASD using HRV measures or electrodermal activity do not support sympathetic autonomic dysfunction associated with autism. In response to tasks, the sympathetic activity goes up, similar to typically developing children, but there is no hyper-arousal.

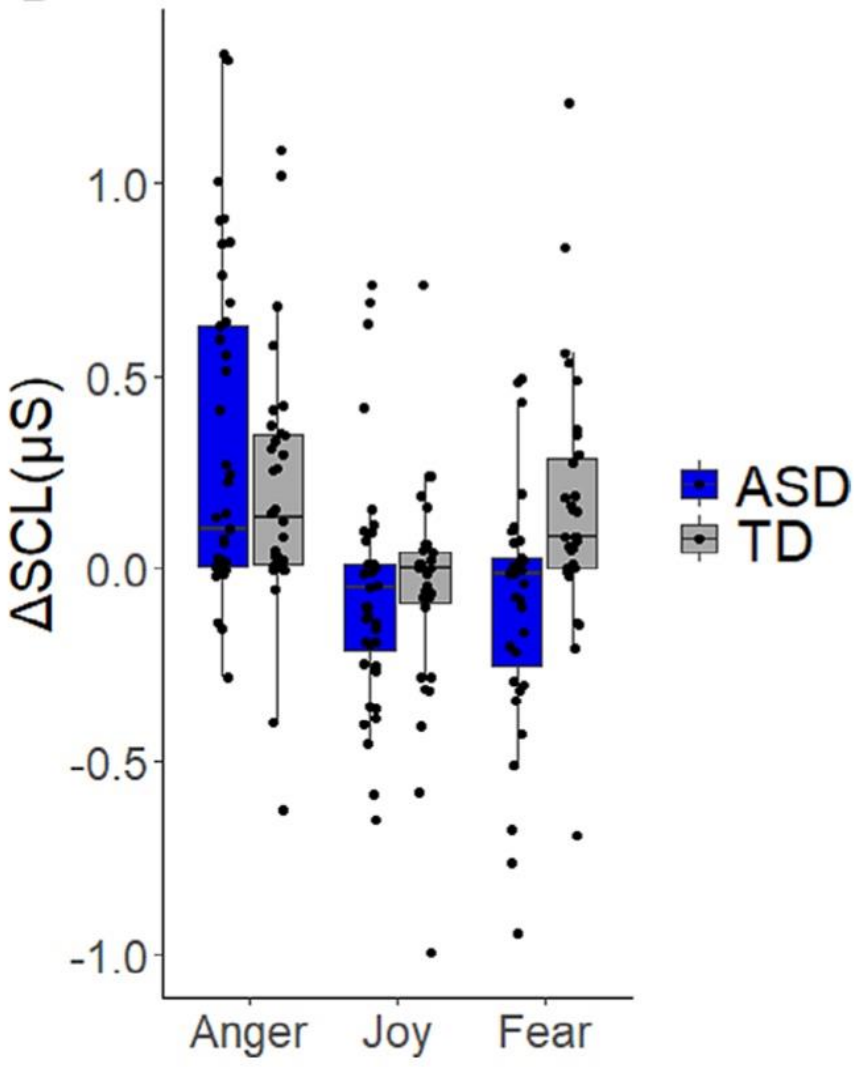

Figure 5.6 Children do not show a significant difference in sympathetic response to stimuli. Expression of skin conductance as a measure of activity in the sympathetic nervous system. From (Vernetti et al., 2020). Note the wide range of values in both the control and ASD groups. Eliciting anger, frustration or joy evoked a similar increase in sympathetic activity in the ASD and control group. In response to a fear-inducing stimulus, the control group exhibited an increase while the ASD group exhibited a decrease in sympathetic activity. However, the scatter plots show that most children with ASD and controls have a response that centers around 0, and most values in the ASD group fall within the range of control values. Hence a correct conclusion is that some children with ASD have a *decreased* arousal response to fear stimuli. The authors did not find a statistically significant difference

in baseline sympathetic values and no correlation between the degree of sympathetic responses and the severity of autism. They conclude that toddlers with ASD should not be labelled as “dysregulated” or “upregulated” with respect to autonomic functioning.

Effect of medication on HRV

Almost all studies involving children with ASD are small, and given that there is a wide range of studied variables, this makes comparison and interpretation difficult. Mathewson et al. (Mathewson, Drmic, Jetha, & Bryson…, 2011) measured RSA and heart rate to evaluate autonomic response to a challenging task, the Stroop test, dividing an adult ASD group based on the usage of antipsychotic medications. Controls were IQ-matched, and no subjects were intellectually impaired. The ASD-medication group had a significantly higher heart rate and lower RSA than both the control and ASD-no-medication group at baseline. Baseline RSA and heart rate were not significantly different between the control and ASD-no-medication groups. Contrary to their expectations, the autonomic responsiveness to the Stroop test was the same for the ASD and control group (Mathewson et al., 2011). Thapa et al. confirmed this in autistic children: no differences in heart rate, RMSSD, nor high-frequency power were observed in children not on psychotropic medication, compared to a control group (Thapa, Pokorski, Ambarchi, & Thomas…, 2021). Hence, medication is likely a major factor in the higher heart rate found in ASD groups. A study involving 616 controls and 1479 adults with anxiety showed that lower RSA in anxious subjects (52.1 vs 45.1 ms; peak - valley method) survived adjustment for possible confounding factors as health indicators and lifestyle, but further adjustment for antidepressant use rendered all associations non-significant (Licht, Geus, & Dyck…, 2009). Hence, drug use is a critical factor affecting HRV.

Autism and co-morbidities

Anxiety

Children with autism, on average, experience a higher level of anxiety than those without ASD (Gillott, Furniss, & Walter, 2001) (Russell & Sofronoff, 2005) (Lau, Leong, Uljarevic, Lerh, & Rodgers…, 2020); however, anxiety is not a diagnostic criterium for autism spectrum disorder (American Association of Psychiatrists, 2021). Anxiety can be a symptom, but it is difficult to differentiate the ‘appropriate’ or ‘normal’ level of anxiety to a stimulus experienced by a neurotypical person vs someone with autism. It cannot be

said that autism *causes* anxiety or vice versa; therefore, it is most appropriate to look at anxiety and autism independently.

A meta-analysis on the relationship between anxiety disorders and controls related to HRV parameters gave mixed results, with many studies finding on average a lower HRV in patients with anxiety disorders but many other studies finding no differences with controls (Chalmers, Quintana, Abbott, & Kemp, 2014).

All studies on ASD children are done, by definition, in experimental settings, and anxiety or stress will play a part in such studies in both controls and children with ASD. Studies on anxiety and autism give mixed conclusions, indicating that some but not all children with ASD have increased anxiety related to specific social stimuli (Jitlina et al., 2017) (Mazurek & Petroski, 2015) (White, Oswald, Ollendick, & Scahill, 2009) (White & Roberson-Nay, 2009) (Guy et al., 2014). Guy et al. reported that correlational analyses from their study indicated that low RSA was driven by factors that were part and perhaps entirely transdiagnostic— namely, symptoms of anxiety (Guy et al., 2014). Hence, some children with a high heart rate and/or low RSA may have, during the experimental conditions, a relatively high level of anxiety. An interesting study on autistic adults using self-reported frequency of autonomic nervous system-related physical health problems found that anxiety and stress but not autistic traits were correlated with autonomic dysfunction (Taylor, Livingston, Callan, Ashwin, & Shah, 2021).

Studies in children with ASD always include stimuli that are thought to activate a stress response. But the response may just reflect the amount of physical activity and the accompanying metabolic demand (Koolhaas et al., 2011). Koolhaas et al. suggest that a true stressor involves uncontrollability and unpredictability (Koolhaas et al., 2011). It is suggested that a stress effect is more related to the recovery of a physiological response than the magnitude of the response (Koolhaas et al., 2011). Children with ASD may be used to finding themselves in a situation that is not desirable, they may have found ways to adapt to it, and this may influence the response to a stimulus.

Parma et al. concluded that “ASD is related to reduced variability in basal sympathetic arousal and vagal modulation which can be taken as markers for inflexible responses (Thayer & Brosschot, 2005) (Parma et al., 2021). This conclusion is not consistent with their data. First, no responses were evaluated, only baseline values. There were no significant differences between control groups and patients with or without anxiety concerning baseline skin conductance, and there were no significant differences in the high-frequency component (RSA) between autistic children with and without anxiety and a control group with anxiety.

Gastrointestinal symptoms.

Compared to typically developing children, there is a significantly higher prevalence of gastrointestinal symptoms in children with ASD (McElhanon, McCracken, Karpen, &

Sharp, 2014), with functional constipation the most common gastrointestinal symptom. The autonomic nervous system plays a critical role in gut motility control. Vagal parasympathetic efferents provide parasympathetic innervation of the upper gastrointestinal tract, while sacral parasympathetic pathways innervate the distal gastrointestinal tract (Brookes, Dinning, & Gladman, 2009) to initiate propulsive contractile activity. Sympathetic nerves inhibit enteric cholinergic excitation to colonic smooth muscle and contract sphincters, contributing to decreased transit that may lead to constipation (Lomax, Sharkey, & Furness, 2010).

Ferguson et al. (Ferguson et al., 2017) investigated the relationship between autonomic nervous system activity and gastrointestinal symptoms in children with autism, finding a significant correlation between lower gastrointestinal tract symptoms, such as constipation and lower parasympathetic tone. This supports the idea that, to a certain extent, lower gastrointestinal motility is controlled by parasympathetic activity (Yuan et al., 2019). Parasympathetic activity at baseline was particularly strongly related to lower gastrointestinal symptoms in participants who reported a co-occurring anxiety disorder. Hence, a subgroup of ASD children may have a low RSA due to gastrointestinal symptoms.

Does measuring HRV parameters in children with ASD have relevance?

Based on heart rate and RSA data, most children with autism do not display autonomic dysfunction. Hence, these parameters should not be studied to learn more about the pathophysiology underlying the symptoms related to the diagnostic criteria of autism. However, if a better understanding of co-morbidities with autonomic dysfunction is to be obtained, it may be worthwhile to study HRV parameters.

How should HRV be measured?

When autonomic functioning is to be assessed in patients with ASD, it is not advisable to only pay attention to RSA, just because it is the focus of the polyvagal theory. A comprehensive assessment should include other parameters as outlined by task forces (Camm, 1996). This should include the Baevsky stress index (Gozhenko, Petrov, & Kovalevska…, 2013) (Baevsky & Chernikova, 2017) (Ali et al., 2021) for sympathetic function. Recently, the Baevsky index has been shown to be a reliable measure of sympathetic activity in the active standing test (Yuan et al., 2020, #63744). Beversdorf reviewed the role of adrenergic antagonists in ASD treatment, and evaluation of their potential use may rely on HRV assessment as well as plasma catecholamine levels (Beversdorf, 2010). A review by Benevides and Lane (2015) suggests that PEP should be used for sympathetic activity, but as we have pointed out, we believe that the evidence indicates that PEP does not measure sympathetic activity associated with task

performance. Benevides and Lane have further suggestions for ANS assessment in children with autism including different models for interpretation (Benevides & Lane, 2015). Some parameters of HRV can be graphically captured using the Poincaré plot. The Poincaré plot is primarily a nonlinear technique, but the most often used descriptors SD1 and SD2 are measuring linear aspects of the heartbeat intervals; they do not add value to existing HRV indexes (Brennan & Palaniswami…, 2001). In particular SD1, which is mathematically equivalent to RMSSD; RMSSD = $\sqrt{2} \times$ SD1 (Guzik, Piskorski, Krauze, & Schneider…, 2007). SD2 is also highly correlated with RMSSD and should therefore not be used as a sympathetic descriptor (Guzik et al., 2007) (Hoshi, Pastre, & Vanderlei…, 2013). It is important to note that if HRV parameters are used to study co-morbidities with autonomic dysfunction, one has to account for covariates that affect autonomic function such as age, sex, body posture at the time of recording, and time of day of the recording (Harteveld et al., 2021). Several studies provide evidence that HRV parameters are different for children who are intellectually impaired (IQ < 70) compared to non-intellectually impaired children (IQ ≥ 70) (Patriquin et al., 2019). However, the appropriateness of subdividing children according to IQ is questionable since intelligence can be expressed and measured in various ways.

Long-term measurements

In addition to the short-term HRV parameters to measure baseline and response to stimuli, long-term 24 hr HRV analysis may reveal important information. Not so much average HRV parameters over 24 hrs since this is very much dependent on activities performed during the day and night, but analysis of events and analysis of HRV during sleep (Hayano & Yuda, 2021). Children with ASD frequently suffer from difficulties falling asleep or nightmares (Verhoeff, Blanken, & Kocevska…, 2018) (Leader, Barrett, Ferrari, & Casburn…, 2021). Research is ongoing to examine HRV descriptors for dynamic changes over time that are not captured by the classic short-term parameters (Hayano & Yuda, 2021). Long-term assessments have the additional advantage of being implemented in a familiar setting.

Reporting absolute values

Lack of reporting absolute values of HRV parameters in the ASD literature is common but makes it difficult to compare studies and relate the findings to overall control values. In some studies, neither absolute values are reported nor comparisons to control values (Patriquin et al., 2019). Any RSA response should also be related to the absolute value at baseline. It is possible that when the hypothesis is tested whether a stimulus is increasing the RSA, a subject with an RSA of 9 ln(ms^2) is less likely to respond in this

way compared to a subject with an RSA of 5 ln(ms^2), because in the first, the parasympathetic nervous system may be in a heightened state of arousal. It is also important to report all individual values. This will show “outliers” that might be clinically highly relevant. In this respect, the bar graphs we present here may not reflect an exact distribution in that they suggest an even distribution of values, but the individual values are not shown in the reported studies. What is needed is knowledge of the distribution of values, hence the reporting of all absolute values in scatter plots. Concerning RSA obtained from HF power, it may be worthwhile to show the distribution of HF power, since RSA is a logarithmic transformation of HF power and as such (designed to) diminish outliers. If data are too extensive to be put in the publication, they can be expressed as violin plots or submitted as supplementary data online.

What are suitable control values?

HRV parameters have a wide range of control values and are very susceptible to circumstances, such as simple body movements. Harteveld et al. studied control values in 4822 children and concluded that the wide range of normal values would cause problems of interpretation for clinical studies (Harteveld et al., 2021). A very small group of typically developing children does not give us a true normal range of control baseline values, assumed to represent general parasympathetic health. A study investigating changes in response to stimuli obviously needs a control group. Comparing the changes in response to stimuli is likely more relevant than focusing on the absolute values in such studies. Responses should also be related to the baseline absolute values.

Mentioning units of measurement

It is common in the ASD-HRV literature not to mention units for HRV parameters. This is unfortunate since this makes comparisons and interpretations by others difficult. For example, numerical values are given to the term “HRV,” but the definition of HRV as a specific autonomic function parameter is variable. Sometimes it is used as equivalent to RMSSD and sometimes used as equivalent to RSA. Sometimes absolute values are used and sometimes logarithmic transformations. RSA is most often derived from the power of the high-frequency range of inter-beat intervals, but sometimes it is measured by subtracting the shortest inter-beat interval during inhalation from the longest inter-beat interval during exhalation. The high-frequency range is most often, but not always, defined as 0.15 – 0.40 Hz, equivalent to the normal breathing frequency range of 8 – 25 breaths per minute. Sometimes the term “normalized units” is used, but it is often not explained how the data are normalized. This results in difficulties of interpretation and may result in inaccurate comparisons between studies. For RSA, it is best first to report the raw values of HF power and determine the distribution of values since we are

emphasizing the recognition of subgroups within an ASD cohort, and it should be noted that the logarithmic transformation from HF power to RSA may obscure “outliers”; it is in fact designed to “normalize” the data, but the “outliers” may constitute a clinically significant subgroup.

HRV studies are always time-consuming and involve patient and parent time. It is, therefore, unfortunate that usually only RSA is measured, no doubt because of its emphasis within the polyvagal theory. To get an optimal picture of HRV, all possible parameters should be reported, including the Baevski index derived from heartbeat intervals.

The polyvagal theory and ASD.

The polyvagal theory proposes that children with ASD have chronic sympathetic activation or a chronically mobilized state (Patriquin et al., 2019), but studies with electrodermal activity do not support this. Electrodermal activity does register sympathetic responses to social activities, but abnormal excitation is not seen. Another proposed measure of chronic sympathetic activation is elevated heart rate. Porges and co-workers make strong statements that fail scrutiny, such as: “In particular, children and adolescents aged 8–18 years with ASD and intellectual impairment have a heart rate that is 20 beats per minute higher than typically developing controls” with reference to (Goodwin et al., 2006). This sounds like a definitive statement about ASD; however, Goodwin et al. report on five children with ASD and five children with normal development, with one normal child having a heart rate of 50 bpm; hence this can hardly be accepted as a definitive statement on ASD. Excess excitation of the sympathetic nervous system is central to the polyvagal autonomic dysfunction theory. The tasks that ASD children are asked to do are designed to emphasize the typical events that the children are deemed to have difficulty with due to ASD. These tasks increase sympathetic activity, as shown by electrodermal activity. Hence the conditions appear to be perfect for showing exaggerated sympathetic arousal, but it is not observed.

The polyvagal theory proposes that children with autism show vagal withdrawal or “chronic mobilization” that would lead to low baseline RSA. RSA is integral to the polyvagal theory. It is proposed to reflect autonomic activity from the nucleus ambiguous involved in heart rate regulation, breathing, and responses involving emotion. Most children with ASD have a baseline RSA that is the same as controls, and there is no evidence that the absolute baseline value of RSA in children with ASD can be considered a sign of autonomic dysfunction. Furthermore, Porges et al. (Porges et al., 2013) propose the idea that children with ASD are unable to display “appropriate” psychophysiological flexibility in response to stimuli due to autonomic inflexibility. Expressly, Porges (1976) indicated that children with ASD may be at one particular autonomic “setting” and are not

able to demonstrate psychophysiological flexibility to stimuli (e.g., appropriate vagal withdrawal to attention-demanding stimuli) (Patriquin et al., 2019). Most studies do not support abnormal RSA responsiveness in children with ASD, which means that either this neural communication involving the nucleus ambiguous is normal in most children with ASD or that RSA is not the best window to observe relevant autonomic functioning in ASD. It is acknowledged that RSA is but one of the windows into autonomic functioning and that other brain areas such as the amygdala and its effect on the functioning of the nucleus ambiguous deserve our attention to understand the physiology behind the behaviours of children with ASD (Toichi & Kamio, 2003) (Schumann, Bauman, & Amaral, 2011) (Patriquin et al., 2019). Furthermore, the hypothalamic pituitary adrenocortical axis and the adrenal medulla are critical players in the response to (potential) stress stimuli in metabolic and cardiovascular preparation of the body to perform behaviour (Koolhaas et al., 2011) (Sapolsky, Romero, & Munck, 2000).

Perspective

In many studies with ASD children, statistical differences in HRV parameters are uncritically deemed to be clinically relevant. Children with ASD are categorized as having inhibited parasympathetic activation and being in a state of chronic vagal withdrawal and heightened sympathetic arousal based on statistical differences between groups that may have no clinical importance. Based on generally accepted control values, almost all children with ASD have a normal heart rate and a normal RSA at baseline, and most children also fall within the control values of the study control group. Hence, there is no evidence that baseline HRV values in children with ASD point to autonomic dysfunction underlying the typical symptoms that define ASD. The autonomic nervous system plays a vital role in children's adjustment to physical stimuli such as standing up, walking, change in outside temperature etc. It is assumed that this is also true for social or emotional stimuli and would be measurable by HRV assessment. Children with ASD often have an atypical reaction to provocations; hence, evaluating autonomic functioning in response to such stimuli would be logical. A stressful social interaction, similar to standing up, usually increases heart rate and decreases RSA (e.g. Figure 5.2). The fact is that in most studies, the autonomic nervous system of children with ASD reacts to social stimuli in this normal manner, very similar to control groups. Interestingly, when RSA goes up in response to a positive, relaxing intervention, it does so similarly in controls and children with ASD (Muscatello et al., 2021). A recent review by (Benevides & Lane, 2015) also concluded that no apparent differences in resting parasympathetic activity emerged from the literature, nor differences in task-related ANS activity (Benevides & Lane, 2015). The *data* from almost all HRV studies on ASD herald the positive news that there is no

evidence of general autonomic dysfunction associated with the typical ASD traits. It is disheartening that most *conclusions* stated in these studies suggest the opposite.

This leaves us with the finding that some children with ASD have a baseline value or a reaction to stimuli that fall outside of the “normal range” being defined as within the 95% confidence interval or a value of less than 1 SD away from the mean. It is supported by many studies that a relatively low RSA or a relatively high heart rate is associated with a comorbidity that is related to autonomic dysfunction, such as anxiety or gastrointestinal motor dysfunctions. Hence, it may be worthwhile to do HRV analysis to identify those children with ASD suspected of having underlying autonomic conditions, e.g., a low RSA may benefit from exercise training to promote healthy parasympathetic reactivity (Fu & Levine, 2018) (Cook & Sandroni, 2018)

6 General discussion

6.1 Main insights obtained into the pathophysiology of our patients

The influence of autonomic activity on gastrointestinal motility dysfunction highlights the importance of the autonomic nervous system in gastrointestinal function. Embryonic development of the spinal cord and vertebrae are linked to development of gut neuronal systems and the development of dorsal root and sympathetic ganglia that are involved in somatosensory and autonomic pathways, respectively, all of which are involved in digestive processes. The thoracic spine is highly involved in the innervation of upper GI motility processes. Dysfunction of autonomic pathways from the thoracolumbar spinal cord may result in the pathophysiology of complex and severe upper GI dysmotility. Spinal conditions and injury can cause thoracic neurogenic impairment, with particular influence on autonomic and sensory pathways, resulting in patients to exhibit severe dysmotility symptoms and impaired quality of life. We have found spinal pathology to be correlated with groups of GI symptoms that are potentially indicative of the location of present spinal pathology. Spinal pathology at the T3-T9 level has been correlated with the experience of nausea, vomiting > 6 hours after eating, postprandial hiccups and abdominal gurgling. Spinal pathology of scoliosis at the T10-L2 level has been correlated with epigastric pain in the form of tightness, sudden onset constipation and nausea. Spinal pathology (non-scoliosis) at the T10-L2 level has been correlated with the experience of postprandial pain in the left lower quadrant of the abdomen with associated nausea.

Non-invasive neuromodulation treatment targeting thoracic spinal nerves has shown to have beneficial effects for patients with symptoms of upper GI dysmotility and has shown improvements in both patient GI symptoms and abdominal pain, particularly in postprandial abdominal pain, sudden-onset constipation, vomiting, abdominal bloating and nausea. Success of TENS treatment provides evidence for the involvement of spinal pathology in complex GI dysmotility and successful treatment of spinal pathology-induced dysmotility symptoms. Further investigation of autonomic functioning via HRV parameters during neuromodulation treatment will help to also provide a better understanding of the involvement of autonomic functioning in the pathophysiology of upper GI dysmotility patients.

6.2 The strengths and major contributions of my research into diagnosis and treatment

The symptoms suggested by this research to be indicative of particular spinal pathology provides guidelines for the future diagnosis of complex GI dysmotility cases with suspected spinal conditions, and supports the GI dysmotility patient population that lack clear diagnosis and clear pathology, yet suffer with a diminished quality of life due to symptoms and limited, unsuccessful treatment options. The traditional diagnosis process

involves GI investigations that often show unremarkable results in complex patients, leading to no diagnosis and little to no response to traditional treatment options, including diet, lifestyle, and pharmacological intervention. Implementation of the questionnaire with careful consideration of these symptoms will suggest primary pathology efficiently and at low cost. Patients with spinal conditions that do not exhibit the dominant symptoms determined here imply other pathology of their condition to be further investigated. Symptom findings may also be used as a reference for studies on future treatments of GI dysmotility, allowing for the investigation of treatments specifically targeting the main pathology of patients' condition and aiming for the best possible patient outcome.

The improvements seen in GI dysmotility symptoms and abdominal pain in response to thoracolumbar TENS treatment has warranted the investigation of TENS as a successful treatment of complex GI dysmotility. Treatment options for complex cases with no clear diagnosis are often unsuccessful, likely due to treatment targeting symptom presentation rather than the primary pathology. Success seen with TENS treatment, particularly in GI symptoms, implies the presence of autonomic pathology such as that seen with spinal conditions, and a potential treatment option for such conditions. This research opens the door to not only TENS treatment, but also other neuromodulation treatments that may be beneficial for the treatment of the main pathology of patient condition, allowing for non-invasive, low-risk and highly accessible treatment options for patients. This research has allowed for a greater understanding of the patient population with complex dysmotility symptoms and has allowed us to determine starting points for future study of spinal pathology and neuromodulation treatment options. Findings of a diagnosis of autism spectrum disorder not being associated with autonomic dysfunction encourages further testing for future autism patients who exhibit symptoms of autonomic dysfunction, such as severe GI dysmotility symptoms, to determine the underlying pathology of their condition.

This research has allowed for the collection of extensive patient background, as recorded by questionnaires, to determine clinical characteristics associated with spinal pathology and ultimately suggest potential symptoms indicative of particular pathology for the future of GI dysmotility diagnosis. This has allowed for better understanding of clinical characteristics of the patient population with complex GI dysmotility that is required for the future of our lab's studies, while doing so on a case-by-case analysis of each patient for individualized treatment. In doing in-depth analysis on individual patients, it allowed for complex patients with non-specific symptoms in a largely heterogenous population to be grouped and defined based on spinal pathology. The grouping of such patients will allow for better investigation into treatment options and characterization of patient conditions. The studies in this thesis have involved the beginning steps to characterizing spinal pathology and potential neuromodulation treatment options. Results have paved

the way for the conduction of future studies, both in the determining of symptoms indicative of spinal pathology and responsive treatment options.

6.3 Limitations of research

Throughout all of the studies in this thesis, the limitation of small patient population size is prevalent. Small sample sizes and heterogeneity of the population make it difficult to make generalized conclusions, such as which spinal pathology TENS has the most beneficial effect on. It was not possible to determine which spinal pathology TENS had the largest effect on, however I conclude that TENS successfully treated symptoms of complex GI dysmotility and abdominal pain with thoracolumbar spinal pathology. Additional studies are required to further investigate the most ideal candidates for neuromodulation treatment. Studies also did not include a patient group with non-spinal pathology, which would be beneficial in investigating the effect of TENS treatment on spinal pathology versus alternative pathology and better identifying the ideal candidate for TENS treatment. Throughout the studies in this thesis, data was reported in a self-assessment model, highly due to limitations and restrictions in place due to the COVID-19 pandemic. Self-assessment models allow the studies to be vulnerable to response bias and some inaccuracies in the data reported. Another limitation involved the lack of placebo or control group in the TENS study. The aim of this study was to determine if TENS treatment would warrant further, in-depth investigation of the effect of TENS on GI dysmotility and autonomic function, which results of symptom improvement justified. The at-home nature of these studies resulted in difficulty in monitoring patient compliance, and difficulty in recruiting participants that were compliant with treatment protocols. It often resulted in lack of questionnaire data for TENS analysis and issues surrounding the treatment protocol. Ultimately, the study findings have shown promising results of TENS treatment for patients with spinal pathology, paving the way for the development of future studies, which are to be conducted with under most efficient protocol.

The final limitation of these studies involved the lack of autonomic functioning assessment and analysis. Due to the COVID-19 pandemic, in-centre testing and treatment was not permitted, resulting in the lack of autonomic information of patients. Autonomic testing would have allowed for the measurement of autonomic function in spinal patients and further validated the presence of spinal pathology-induced autonomic dysregulation or dysfunction, leading to GI dysmotility. Completing this autonomic testing prior to, during, and after TENS treatment would allow for the monitoring of the effect of TENS on autonomic function and bring further insight onto the underlying mechanisms of TENS neuromodulation treatment.

6.4 Future research that would be beneficial for further understanding of diagnosis and treatment of patients with complex GI motility dysfunction

To further the understanding of the diagnosis and treatment of patients with complex GI motility dysfunction, it is essential for future research to investigate symptoms that may be correlated with spinal pathology, particularly specific spinal conditions. In this study, scoliosis-induced pathology at the T10-L2 level was found to have different symptom presentation than other non-scoliosis spinal conditions within the same thoracolumbar region, warranting future investigations with subgroups of different spinal conditions. Determining symptoms related to particular spinal conditions and spinal locations would allow for initial questionnaire assessment results to point to specific pathology, which would ultimately point towards the best treatment options for patients' particular pathology. Future research should also look at the effect of TENS on particular spinal pathology or conditions. In this thesis, we see that TENS has had a successful effect on dominant GI symptoms such as nausea, however it would be highly beneficial to further subgroup subjects to determine if the effect of TENS changes based on specific spinal pathology. This would not only allow for better understanding of the mechanism of TENS, but also for the ideal candidate for treatment. Including autonomic assessments for spinal patients in future research is essential for determining the relationships between spinal pathology, autonomic dysfunction, and GI dysmotility symptoms.

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Appendix A

Welcome! Please answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

Section A: Welcome

A1. Please enter your full name below:

A2. Is this your first assessment?

- Yes ☐
- No ☐

A3. Please select the stage of your TENS treatment:

- Before TENS ☐
- 4 weeks of TENS ☐
- 2 months of TENS ☐
- 3 months of TENS ☐
- 4 months of TENS ☐
- 5 months of TENS ☐
- 6 months of TENS ☐
- 7 months of TENS ☐
- 8 months of TENS ☐
- 9 months of TENS ☐
- 10 months of TENS ☐
- 11 months of TENS ☐
- 12 months of TENS ☐

A4. **Please describe how consistently you do your TENS treatment (Ex. twice a day, once a day, every other day, etc.)**

Section B: General Health

B1. **Have you ever been diagnosed with COVID-19?**

- Yes ☐
- No ☐
- Suspected ☐

B2. **Have you ever had surgery?**

- Yes ☐
- No ☐

B3. **Please describe what your surgery was and when you had it:**

B4. **Have you had any weight gain since your last assessment?**

- Yes ☐
- No ☐

B5. **Please type your weight gain in lbs**

B6. Have you had any weight loss since your last assessment?

- ☐ Yes
- ☐ No

B7. Please type your weight loss in lbs

B8. Have you experienced difficulties/impairment in your daily living activities (ex. walking, getting dressed, driving, etc.)

- ☐ Yes
- ☐ No

B9. Please indicate the frequency of your daily activity impairment.

- ☐ 1 - Infrequent (<30% of the time)
- ☐ 2 - Frequent (30-60% of the time)
- ☐ 3 - Very Frequent (>60% of the time)

B10. Please indicate the severity of your daily activity impairment.

- ☐ 1 – Mild (1-3 on pain scale of 10)
- ☐ 2 – Moderate (4-6 on pain scale of 10)
- ☐ 3 – Severe (7-8 on pain scale of 10)
- ☐ 4 – Very Severe (9-10 on pain scale of 10)

B11. Have you had to take any sick days/leave from work due to symptoms?

- ☐ No
- ☐ Rarely (1-2 days per month)
- ☐ Often (1 day per week)
- ☐ Very Often (2+ days per week)
- ☐ On Full-Time Leave

B12. Please note any past or present life experiences that put a physical strain on your body (example: sports, accident, injury, etc.)

B13. How physically demanding is your occupation/job?

- ☐ Low physical demand (mostly sitting - ex. office work)
- ☐ Moderate physical demand (on your feet most of the day - ex. nursing)
- ☐ High physical demand (ex. construction)

B14. Have you had any changes in your medication since your last assessment?

- ☐ Yes
- ☐ No

B15. Please note the changes in your medication below (medication, dosage, etc.)

B16. Please list your current medications and dosages:

Section C: Head

This section asks you about symptoms related to your head. Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate the frequency and severity you experienced since your last assesment. If this is your first assessment, please indicate based on if have ever experienced the symptom.

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

C1. How frequent and severe have each of these symptoms been since your last assessment?Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Headaches/Migraine	☐	☐	☐
Nausea	☐	☐	☐
Dizziness	☐	☐	☐
Anxiety	☐	☐	☐
Depression	☐	☐	☐
Fear	☐	☐	☐
Worry	☐	☐	☐
Seizures	☐	☐	☐
Loss of appetite	☐	☐	☐
Lack of focus	☐	☐	☐
Difficult sleeping	☐	☐	☐
Loss of hearing	☐	☐	☐
Vision change	☐	☐	☐

C2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Headaches/Migraine	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐
Anxiety	☐	☐	☐	☐
Depression	☐	☐	☐	☐
Fear	☐	☐	☐	☐
Worry	☐	☐	☐	☐
Seizures	☐	☐	☐	☐
Loss of appetite	☐	☐	☐	☐
Lack of focus	☐	☐	☐	☐
Difficult sleeping	☐	☐	☐	☐
Loss of hearing	☐	☐	☐	☐
Vision change	☐	☐	☐	☐

C3. Please note if you have experienced any stressful event(s) and/or head injury since your last assessment, and its severity.

	0 - Absent	1 - Mild	2 - Moderate	3 - Severe	4 - Very Severe
Stressful Event(s)	☐	☐	☐	☐	☐
Head Injury	☐	☐	☐	☐	☐

C4. Please note if you have ever experienced any significant stressful event(s) and/or head injury(s), and its severity.

	1 - Mild	2 - Moderate	3 - Severe	4 - Very Severe
Stressful Event(s)	☐	☐	☐	☐
Head Injury(s)	☐	☐	☐	☐

C5. Please provide any additional information about your stressful event(s) and/or head injury(s):

C6. Have you experienced any other symptom(s) related to your head not listed above?

Yes ☐

No ☐

C7. Please list other symptom(s) related to your head below

Symptom 1 ☐

Comment

Symptom 2 ☐

Comment

Symptom 3 ☐

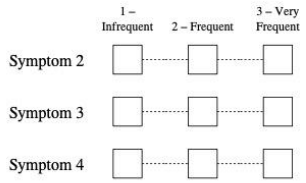
Comment

Symptom 4 ☐

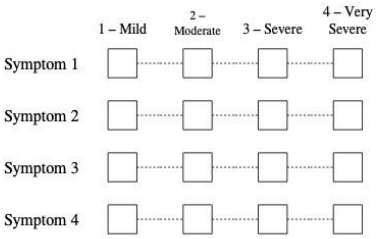
Comment

C8. Please note the frequency and severity of each additional symptom you listed. Frequency

	1 – Infrequent	2 – Frequent	3 – Very Frequent
Symptom 1	☐	☐	☐



C9. Please note the frequency and severity of each additional symptom you listed. Severity



Section D: Neck

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

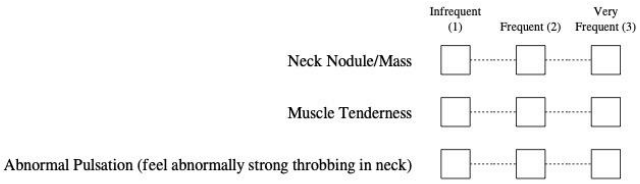
If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

D1. How frequent and severe have each of these symptoms been since your last assessment?Frequency



D2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Neck Nodule/Mass	☐	☐	☐	☐
Muscle Tenderness	☐	☐	☐	☐
Abnormal Pulsation (feel abnormally strong throbbing in neck)	☐	☐	☐	☐

D3. Have you experienced any other symptom(s) related to your neck not listed above?

☐ Yes

☐ No

D4. Please list other symptom(s) related to your neck below

Symptom 1

Comment

Symptom 2

Comment

Symptom 3

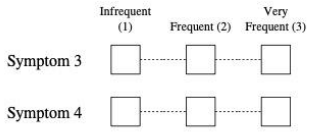
Comment

Symptom 4

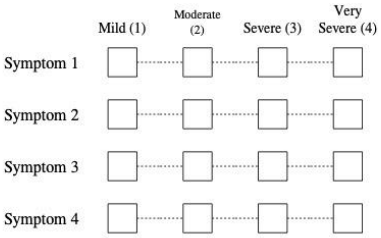
Comment

D5. Please note the frequency and severity of each additional symptom you listed. Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Symptom 1	☐	☐	☐
Symptom 2	☐	☐	☐



D6. Please note the frequency and severity of each additional symptom you listed. Severity



Section E: Shoulder

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

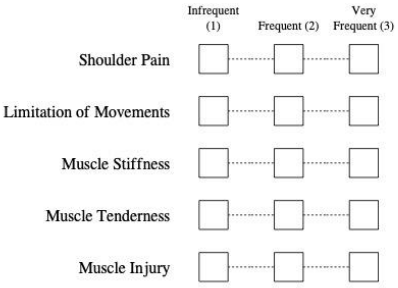
If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

E1. How frequent and severe have each of these symptoms been since your last assessment?Frequency



E2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Shoulder Pain	☐	☐	☐	☐
Limitation of Movements	☐	☐	☐	☐
Muscle Stiffness	☐	☐	☐	☐
Muscle Tenderness	☐	☐	☐	☐
Muscle Injury	☐	☐	☐	☐

E3. Have you had any treatment to your shoulder, such as physiotherapy or injections?

Yes ☐

No ☐

E4. Please note what the treatment to your shoulder was and how frequently you were/are treated:

E5. Have you experienced any other symptom(s) related to your shoulder not listed above?

Yes ☐

No ☐

E6. Please list other symptom(s) related to your shoulder below

Symptom 1

Comment

Symptom 2

Comment

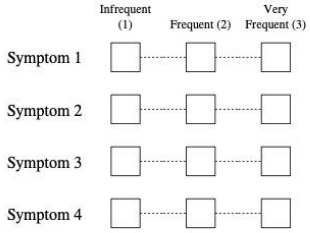
Symptom 3

Comment

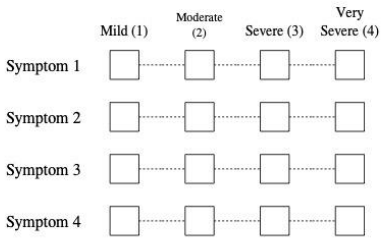
Symptom 4

Comment

E7. Please note the frequency and severity of each additional symptom you listed. Frequency



E8. Please note the frequency and severity of each additional symptom you listed. Severity



Section F: Mouth/Throat

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

F1. How frequent and severe have each of these symptoms been since your last assessment?Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Dry mouth	☐	☐	☐
Loss of taste	☐	☐	☐
Blisters in the mouth	☐	☐	☐
Excessive saliva secretion	☐	☐	☐
Globus sensation (feels like a lump while not eating)	☐	☐	☐
Frequent throat clearing	☐	☐	☐
Difficulty of initiating swallow	☐	☐	☐
Choking	☐	☐	☐
Food gets stuck at the throat	☐	☐	☐
Eating-associated coughing	☐	☐	☐
Aspiration during sleeping	☐	☐	☐
Swelling	☐	☐	☐
Difficulty of breathing	☐	☐	☐
Throat tightness	☐	☐	☐
Throat spasm	☐	☐	☐
Throat bleeding	☐	☐	☐

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Regurgitation (food coming back to the throat)	☐	☐	☐
Vomiting food soon after eating (within 1 hour)	☐	☐	☐
Vomiting food you consumed over 6 hours ago	☐	☐	☐
Blood in vomit	☐	☐	☐
Black or brown colour vomit (except original food colour)	☐	☐	☐
Difficulty of finishing one meal	☐	☐	☐

F2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Dry mouth	☐	☐	☐	☐
Loss of taste	☐	☐	☐	☐
Blisters in the mouth	☐	☐	☐	☐
Excessive saliva secretion	☐	☐	☐	☐
Globus sensation (feels like a lump while not eating)	☐	☐	☐	☐
Frequent throat clearing	☐	☐	☐	☐
Difficulty of initiating swallow	☐	☐	☐	☐
Choking	☐	☐	☐	☐
Food gets stuck at the throat	☐	☐	☐	☐
Eating-associated coughing	☐	☐	☐	☐
Aspiration during sleeping	☐	☐	☐	☐
Swelling	☐	☐	☐	☐
Difficulty of breathing	☐	☐	☐	☐
Throat tightness	☐	☐	☐	☐
Throat spasm	☐	☐	☐	☐
Throat bleeding	☐	☐	☐	☐
Regurgitation (food coming back to the throat)	☐	☐	☐	☐
Vomiting food soon after eating (within 1 hour)	☐	☐	☐	☐

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Vomiting food you consumed over 6 hours ago	☐	☐	☐	☐
Blood in vomit	☐	☐	☐	☐
Black or brown colour vomit (except original food colour)	☐	☐	☐	☐
Difficulty of finishing one meal	☐	☐	☐	☐

F3. Have you experienced any other symptom(s) related to your mouth/throat not listed above?

Yes ☐

No ☐

F4. Please list other symptom(s) related to your mouth/throat below

Symptom 1 ☐

Comment

Symptom 2 ☐

Comment

Symptom 3 ☐

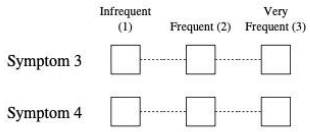
Comment

Symptom 4 ☐

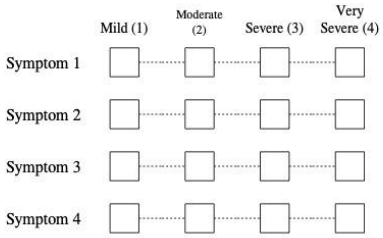
Comment

F5. Please note the frequency and severity of each additional symptom you listed. Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Symptom 1	☐	☐	☐
Symptom 2	☐	☐	☐



F6. Please note the frequency and severity of each additional symptom you listed. Severity



F7. Please describe the features of your nausea and/or vomiting (how long it lasts, what it looks like, triggers such as food, stress, etc.)

Section G: Chest

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

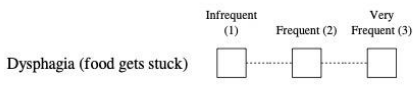
If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

G1. How frequent and severe have each of these symptoms been since your last assessment?Frequency



	Infrequent (1)	Frequent (2)	Very Frequent (3)
Heartburn	☐	☐	☐
Non-cardiac chest pain/Esophageal spasm	☐	☐	☐
Abnormal sensation (such as vibration)	☐	☐	☐
Spontaneous hiccups	☐	☐	☐
Hiccups after eating	☐	☐	☐
Regurgitation after eating	☐	☐	☐
Breathing limitation due to chest discomfort/pain	☐	☐	☐
Upper back pain	☐	☐	☐
Upper back tenderness	☐	☐	☐
Upper back/chest injury	☐	☐	☐

G2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Dysphagia (food gets stuck)	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Non-cardiac chest pain/Esophageal spasm	☐	☐	☐	☐
Abnormal sensation (such as vibration)	☐	☐	☐	☐
Spontaneous hiccups	☐	☐	☐	☐
Hiccups after eating	☐	☐	☐	☐
Regurgitation after eating	☐	☐	☐	☐
Breathing limitation due to chest discomfort/pain	☐	☐	☐	☐
Upper back pain	☐	☐	☐	☐
Upper back tenderness	☐	☐	☐	☐
Upper back/chest injury	☐	☐	☐	☐

G3. **If you experience dysphagia (food gets stuck when swallowing), list any solution(s) you use to help**

G4. **If you experience non-cardiac chest pain/esophageal spasm, list any solution(s) you use to help**

G5. **Have you had any treatments, such as injections or implants, to your chest?**

Yes ☐

No ☐

G6. **Please note what the treatment to your chest was and how frequently you were/are treated:**

G7. **Have you experienced any other symptom(s) related to your chest not listed above?**

Yes ☐

No ☐

G8. **Please list other symptom(s) related to your chest below**

Symptom 1 ☐

Comment

Symptom 2

Comment

Symptom 3

Comment

Symptom 4

Comment

G9. Please note the frequency and severity of each additional symptom you listed. Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Symptom 1	☐	☐	☐
Symptom 2	☐	☐	☐
Symptom 3	☐	☐	☐
Symptom 4	☐	☐	☐

G10. Please note the frequency and severity of each additional symptom you listed. Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Symptom 1	☐	☐	☐	☐
Symptom 2	☐	☐	☐	☐
Symptom 3	☐	☐	☐	☐
Symptom 4	☐	☐	☐	☐

Section H: Abdomen

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

H1. Have you experienced any constipation (no spontaneous bowel movements for more than 3 consecutive days or large difficulty/straining when passing bowel movements)

- ☐ Yes
- ☐ No

H2. Please note the frequency of your constipation

- ☐ Infrequent (1)
- ☐ Frequent (2)
- ☐ Very Frequent (3)

H3. Have you experienced any fecal incontinence (leakage of stool)?

- ☐ Yes
- ☐ No

H4. Please note the frequency of your fecal incontinence (leakage of stool)

- ☐ Infrequent (1)
- ☐ Frequent (2)
- ☐ Very Frequent (3)

H5. **Please describe your bowel habits (frequency of bowel movements, what your stool looks like, difficulties passing gas, etc.):**

H6. **Please refer to the Bristol stool chart and type your answer below.**

The shape of the stool is:

H7. **How frequent and severe have each of these symptoms been since your last assessment?Frequency**

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Persistent abdominal pain	☐	☐	☐
Intermittent abdominal pain	☐	☐	☐
Abdominal discomfort	☐	☐	☐
Abdominal cramping	☐	☐	☐
Abdominal gurgling	☐	☐	☐
Abdominal bloating	☐	☐	☐
Abdominal fullness with increased gas production	☐	☐	☐
Nocturnal abdominal pain	☐	☐	☐
Abdominal pain with associated nausea and vomiting	☐	☐	☐
Abdominal pain with bowel urgency	☐	☐	☐
Abdominal pain with increased frequency of bowel movements	☐	☐	☐
Early Satiety (feeling full)	☐	☐	☐

H8. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Persistent abdominal pain	☐	☐	☐	☐
Intermittent abdominal pain	☐	☐	☐	☐
Abdominal discomfort	☐	☐	☐	☐
Abdominal cramping	☐	☐	☐	☐
Abdominal gurgling	☐	☐	☐	☐
Abdominal bloating	☐	☐	☐	☐
Abdominal fullness with increased gas production	☐	☐	☐	☐
Nocturnal abdominal pain	☐	☐	☐	☐
Abdominal pain with associated nausea and vomiting	☐	☐	☐	☐
Abdominal pain with bowel urgency	☐	☐	☐	☐
Abdominal pain with increased frequency of bowel movements	☐	☐	☐	☐
Early Satiety (feeling full)	☐	☐	☐	☐

H9. If you experience abdominal gurgling, please describe its location.

Section I: Abdominal Symptom Location

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

I1.

Please note the frequency and severity of your abdominal pain in each location of the abdomen

Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Generalized Abdomen	☐	☐	☐
Right Upper Quadrant	☐	☐	☐
Left Upper Quadrant	☐	☐	☐
Right Lower Quadrant	☐	☐	☐
Left Lower Quadrant	☐	☐	☐

I2.

Please note the frequency and severity of your abdominal pain in each location of the abdomen

Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Generalized Abdomen	☐	☐	☐	☐
Right Upper Quadrant	☐	☐	☐	☐
Left Upper Quadrant	☐	☐	☐	☐

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Right Lower Quadrant	☐	☐	☐	☐
Left Lower Quadrant	☐	☐	☐	☐

I3. Please describe the following features of your generalized abdominal pain

Type of Pain (ex. sharp, dull, burning, etc.)

How Long Pain Lasts (hours)

What Makes Pain Better or Worse (after eating, before bowel movements, etc.)

I4. Please describe the following features of your right upper quadrant abdominal pain

Type of Pain (ex. sharp, dull, burning, etc.)

How Long Pain Lasts (hours)

What Makes Pain Better or Worse (after eating, before bowel movements, etc.)

I5. Please describe the following features of your left upper quadrant abdominal pain

Type of Pain (ex. sharp, dull, burning, etc.)

How Long Pain Lasts (hours)

What Makes Pain Better or Worse (after eating, before bowel movements, etc.)

I6. Please describe the following features of your right lower quadrant abdominal pain

Type of Pain (ex. sharp, dull, burning, etc.)

How Long Pain Lasts (hours)

What Makes Pain Better or Worse (after eating, before bowel movements, etc.)

I7. Please describe the following features of your left lower quadrant abdominal pain

Type of Pain (ex. sharp, dull, burning, etc.)

How Long Pain Lasts (hours)

What Makes Pain Better or Worse (after eating, before bowel movements, etc.)

I8. Please note the frequency and severity of pain in other regions that are associated with or radiate from your abdominal pain (occur at the same time). Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Upper Back	☐	☐	☐
Lower Back	☐	☐	☐
Shoulder(s)	☐	☐	☐
Chest	☐	☐	☐
Neck	☐	☐	☐
Jaw	☐	☐	☐
Leg(s)	☐	☐	☐
Pelvic Region	☐	☐	☐

I9. Please note the frequency and severity of pain in other regions that are associated with or radiate from your abdominal pain (occur at the same time). Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Upper Back	☐	☐	☐	☐
Lower Back	☐	☐	☐	☐
Shoulder(s)	☐	☐	☐	☐
Chest	☐	☐	☐	☐
Neck	☐	☐	☐	☐
Jaw	☐	☐	☐	☐
Leg(s)	☐	☐	☐	☐
Pelvic Region	☐	☐	☐	☐

Section J: Back/Spine

If you have not had the symptom, leave the question as 'No Answer'.

If the symptom occurred infrequently (60% of the time), check 3.

If the symptom seemed mild (1-3 pain scale out of 10), check 1.

If the symptom seemed moderate (4-6 pain scale out of 10), check 2.

If the symptom seemed severe (7-8 pain scale out of 10), check 3.

If the symptom seemed very severe (9-10 pain scale out of 10), check 4.

J1. How frequent and severe have each of these symptoms been since your last assessment?Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Neck pain	☐	☐	☐
Muscle stiffness	☐	☐	☐
Limitation of movements	☐	☐	☐
Muscle tenderness	☐	☐	☐
Back/Spine injury	☐	☐	☐

J2. How frequent and severe have each of these symptoms been since your last assessment?Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Neck pain	☐	☐	☐	☐
Muscle stiffness	☐	☐	☐	☐
Limitation of movements	☐	☐	☐	☐
Muscle tenderness	☐	☐	☐	☐
Back/Spine injury	☐	☐	☐	☐

J3. **Please describe your back/spine injury (type of injury, where on your back/spine the injury is, when the injury occured, etc.)**

J4. **Have you had any treatment to your back/spine, such as physiotherapy or injections?**

Yes ☐

No ☐

J5. **Please note what the treatment to your back/spine was and how frequently you are/were treated:**

J6. **Have you experienced any other symptom(s) related to your back/spine not listed above?**

Yes ☐

No ☐

J7. **Please list other symptom(s) related to your back/spine below**

Symptom 1 ☐

Comment

Symptom 2 ☐

Comment

Symptom 3

Comment

Symptom 4

Comment

J8. Please note the frequency and severity of each additional symptom you listed. Frequency

	Infrequent (1)	Frequent (2)	Very Frequent (3)
Symptom 1	☐	☐	☐
Symptom 2	☐	☐	☐
Symptom 3	☐	☐	☐
Symptom 4	☐	☐	☐

J9. Please note the frequency and severity of each additional symptom you listed. Severity

	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Symptom 1	☐	☐	☐	☐
Symptom 2	☐	☐	☐	☐
Symptom 3	☐	☐	☐	☐
Symptom 4	☐	☐	☐	☐

Section K: Additional Symptoms

K1. If you have any other symptom(s) that this questionnaire has not outlined that you would like to mention, please note below:

Appendix B

At-Home TENS Virtual Training Protocol

Step 1: Prepare the patient for treatment in the clinic or (if this is not possible) over a virtual video call. This involves having the patient find a quiet area, where they can be comfortably seated for the treatment. Ensure that the patient has read through the instruction manual for the specific TENS device that they are using, and review all risks, benefits and contraindications before continuing to the next steps. TENS training in a virtual setting brings benefits to patients, such as elimination of travel time and costs. This allows for the treatment of patients that may have geographical or travel limitations. Virtual training also adheres to restrictions due to the COVID-19 pandemic, allowing for full and unaffected treatment of patients regardless of current restrictions.

Step 2: Review operating instructions of device. Insert batteries into the device, if needed. Insert the lead wires into the lead channel sockets on the device, then insert each of the lead wire pins into an electrode pad.

Step 3: Review placement of electrode pads. Ensure the device is off. Area of skin for electrode placement should be clean and dry. Patients should be wearing loose clothing to easily lift and expose and show their spine on camera when necessary. Share screen to a graphic outlining the electrode placement for patient to refer to. Also provide landmarks to help patient identify their anatomy, such as C7 being the most prominent boney protrusion at the back of the neck. Electrode placement is guided via video call with verbal prompting. If patients are completing the electrode placements independently, have them face their exposed spine to the camera, while we guide the placement verbally, with assistance from graphics. If patients are completing the electrode placement with assistance from another person, have that person be present for this duration of the training and guide them verbally and with the assistance of graphics. Each channel of the TENS device is attached to two electrodes – one positively charged (anode) and one negatively charged (cathode). The anode is the red electrode, while the cathode is the black electrode. The anode and cathode of a channel should be placed parallel to the spine (approximately 1cm lateral to the spine), with the anode placed vertically, approximately 1cm above the cathode. Electrode pads should be flat against the skin. Electrode placement is to the left and right (paravertebral area) of the spine at level T5-L2.

Step 4: Set up stimulation parameters. Have patient turn on the device via the ON/OFF button. Select the ‘Normal’ mode by pressing the ‘Mode’ control button. Press the ‘Set’ control button to set appropriate stimulation parameters, including pulse frequency, pulse width and duration. Have patients increase the intensity of each channel, ensuring that

each channel is set to the same intensity level. Increase the intensity to the maximal tolerance level, then decrease by 1-2 levels.

Step 5: Perform experimental treatment for 5-10 minutes via video call. Patient should be in a seated position and report any discomfort, any feedback for how they feel (experience and/or symptoms) and the level of intensity being used for the treatment.

Step 6: Review any precautions with the patient, such as that patients may turn off the device at any time during treatment if they feel necessary. Other precautions include contacting us or the family physician if the development of new symptoms occurs, which may or may not be related to TENS treatment.

Step 7: Review finishing a treatment session. Once the treatment session duration is complete, turn off the device. Lift the edge of the electrode pad and gently peel off the body in the direction of hair growth. Place the electrode pad firmly back on the plastic lining for re-use and remove the wires from the electrodes. Electrode pads may be re-used 3-4 times, so long as the adhesive properties still allow for firm and flat placement on the skin.

Patients are to use consistent stimulation parameters to ensure the stimulation of neural pathways that may lead to beneficial effects on symptoms of GI dysmotility. Stimulation is set to 'Normal' mode, where there is continuous stimulation. Pulse frequency, or the number of pulses delivered per second, is set at 16 Hz. Pulse width is set at 50 msec, and treatment time is set at 15 minutes. The stimulation level of intensity should be individualized patient-to-patient. The stimulation should feel strong, but not painful. Patients should increase the stimulation intensity to the strongest level tolerable, then decrease it 1 level. All channels should be increased to the same intensity level during treatment. Intensity level may be modified on a treatment-to-treatment basis in the case of increased tolerance or increased sensitivity. Total treatment duration is 4 months.

Monitoring of patients who decided to take part in the study

To monitor the treatment, patients were asked to complete an online, self-report questionnaire developed to assess GI symptoms and quality of life, both before and during TENS treatment of the thoracolumbar spine. The assessment was conducted before and every 4 weeks into the treatment to track and monitor changes. The questionnaire determined neurological symptoms that were used to deduce pathophysiology of their GI dysmotility and evaluate whether the treatment alleviated their GI symptoms.

Outcomes and Data Analysis

Outcomes were quantified as described below. We considered a change in the score by 20% in the direction of improvement an indication of success of treatment, although we hypothesized much higher scores. Since this was the first time that a study like this was done, we could not go to the literature for guidance and that is why we consider this a preliminary feasibility study.

Primary outcome: improvement in abdominal and most severe GI symptoms
Measured as the product of the symptom's score of the questionnaire. Abdominal symptoms will improve with a decrease in score from as high as 12 (most frequent and severe) towards 0 (least frequent and severe).

Questionnaire Scoring
The symptoms scores are determined as follows related to the GI questionnaire.

If a symptom occurred infrequently (<30% of the time), it is scored as 1.
If the symptom occurred frequently (30-60% of the time), it is scored as 2.
If the symptom occurred very frequently (>60% of the time), it is scored as 3.

If the symptom was mild severity (1-3 pain scale out of 10), it is scored 1.
If the symptom was moderate severity (4-6 pain scale out of 10), it is scored 2.
If the symptom was severe (7-8 pain scale out of 10), it is scored 3.
If the symptom was very severe (9-10 pain scale out of 10), it is scored 4.

To score each individual symptom, the product of the scored frequency and severity of that particular symptom is calculated. The product of these scores is the score of the symptom. For example, if the frequency of heartburn is 'Frequent' (score of 2) and the severity is 'Severe' (score of 3), the overall score for heartburn is 6.

For each section of the questionnaire (Head symptoms, Chest symptoms, Abdominal Symptoms…etc.), the sum of each individually scored symptom (as calculated above) is calculated to get the total score for that section. For example, if the score of heartburn is 6 and the score of spontaneous hiccups is 4, the total score for Chest Symptoms is 10. The severity of constipation and fecal incontinence is scored based only on the frequency of the symptom. If the symptom was very frequent (>60% of the time) it was scored as 3 (severe). If the symptom was frequent (30-60% of the time), it was scored as 2 (moderate severity). If the symptom was infrequent (<30% of the time) it was scored as 1 (mild severity). If the symptom was absent, it was scored as 0. The patients are asked to fill in the questionnaires after 1 and 2 and 3 and 4 months of treatment.