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Traumatic stress and the autonomic brain-gut connection in development: Polyvagal Theory as an integrative framework for psychosocial and gastrointestinal pathology

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Abstract

A range of psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder frequently co-occur with functional gastrointestinal (GI) disorders. Risk of these pathologies is particularly high in those with a history of trauma, abuse, and chronic stress. These scientific findings and rising awareness within the health-care profession give rise to a need for an integrative framework to understand the developmental mechanisms that give rise to these observations. In this paper, we introduce a plausible explanatory framework, based on the Polyvagal Theory (Porges, *Psychophysiology*, **32**, 301–318, 1995; Porges, *International Journal of Psychophysiology*, **42**, 123–146, 2001; Porges, *Biological Psychology*, **74**, 116–143, 2007), which describes how evolution impacted the structure and function of the autonomic nervous system (ANS). The Polyvagal Theory provides organizing principles for understanding the development of adaptive diversity in homeostatic, threat-response, and psychosocial functions that contribute to pathology. Using these principles, we outline possible mechanisms that promote and maintain socioemotional and GI dysfunction and review their implications for therapeutic targets.

KEYWORDS
autonomic nervous system, brain-gut axis, Polyvagal Theory, stress, trauma

1 | COMORBIDITY OF PSYCHIATRIC AND GI TRACT PATHOLOGY AND THEIR RELATION TO TRAUMA

Functional gastrointestinal (GI) disorders are highly prevalent, occurring in 10%–20% of population worldwide (Saito, Schoenfeld, & Locke III, 2002; Chang, Lu, & Chen, 2010; Lewis, Palsson, Whitehead, & van Tilburg, 2016). These disorders constitute the primary reason for GI referral in pediatric tertiary care centers (Rouster, Karpinski, Silver, Monagas, & Hyman, 2016) and do not respond well to gut-targeted drug therapies (Drossman et al., 2018; Sobin, Heinrich, & Drossman, 2017). They encompass a range of problems with digestion, defecation, abdominal pain, vomiting, nausea, and swallowing without an identifiable structural pathology. Some specific pain-associated functional GI diagnoses include irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain.

Functional GI disorders frequently co-occur with psychiatric diagnoses marked by irritability, fearfulness, hypervigilance, and physiological mobilization (including respiratory and cardiac symptoms). These GI-psychiatric comorbidities are seen across a range of psychiatric diagnoses such as anxiety disorders, depression, and Post-Traumatic Stress Disorder (PTSD; Whitehead, Palsson, & Jones, 2002; Henningsen, Zimmerman, & Sattel, 2003; Mussell et al., 2008; Pacella, Hruska, & Delahanty, 2013; Van Oudenhove, 2016; Tarbell & Li, 2008; Tarbell, Shaltout, Wagoner, Diz, & Fortunato, 2014; Hejazi & McCallum, 2014; Sun, Ke, & Wang, 2015). We propose that these comorbidities may reflect an evolutionarily influenced brain-body state that sensitizes digestive and socioemotional sensory-motor processes toward danger or life-threat responses. This would suggest that GI and socioemotional problems could have a common neurobiological core triggered by acute and chronic threats through development.

Trauma and abuse history promotes anxiety and depression, findings supported by prospective studies (Li, D'Arcy, & Meng, 2016; Norman et al., 2012). The diagnosis of PTSD subsumes several symptoms associated with anxiety and depression, and is dependent on the identification of a traumatic trigger. There is also mounting evidence that trauma experiences are related to the etiology of functional GI problems. Childhood sexual abuse and rape increase the risk for functional GI disorders (for reviews and meta-analyses see Leserman, 2005; Paras et al., 2009; Irish, Kobayashi, & Delahanty, 2009) and these effects are also observed in adults with early life exposure to severe wartime conditions (Klooker et al., 2009). IBS patients with a history of abuse have elevated symptom severity, symptom quantity, and visceral sensitivity (Drossman, 2011; Grinsvall, Törnblom, Tack, Van Oudenhove, & Simrén, 2018). Animal studies provide experimental support that chronic (e.g., repeated maternal separation) and acute early life stressors induce long-term sensory and motor digestive changes consistent with IBS symptoms (e.g., hyperalgesia, alterations in bowel movements; O'Mahony, Hyland, Dinan, & Cryan, 2011; Vannucchi & Evangelista, 2018).

However, trauma history is often undocumented by GI specialists and undetected as a contributor to mental health. Potentially traumatic experiences—such as physical violence, sexual assault, and abuse—are common (Kessler et al., 2017), but many trauma survivors do not disclose their experiences to authorities or close others (e.g., Finkelhor, Hotaling, Lewis, & Smith, 1990; Jeffreys, Leibowitz, Finley, & Arar, 2010; also see review in London, Bruck, Wright, & Ceci, 2008) and do not seek psychiatric care despite trauma-related symptoms. In a survey conducted across 26 countries, fewer than half of respondents who meet criteria for PTSD reported seeking treatment for it (Koenen et al., 2017). A meta-analysis spanning over 6,000 individuals estimated that 18%–39% of patients in secondary-care mental health services have undetected PTSD and are likely being treated for diagnoses secondary to trauma (Zammit et al., 2018). In addition, rates of physical and sexual trauma among gastroenterology patients are high, with these trauma survivors displaying higher pain and functional disability (Drossman et al., 1990; Leserman et al., 1996). Yet, conversations about trauma history with care providers are rare and most trauma histories go unreported to GI specialists (Drossman, 2011; Drossman et al., 1990).

These convergent findings highlight the comorbidity of mood and anxiety disorders with GI problems, their shared association with trauma, and the need to understand the mechanisms that lead to pathology and to inform treatment. To meet these goals, there is a need for an integrative framework that unifies these findings to inform clinicians and researchers. Here, we present an explanatory framework for these observations, informed by the function of the autonomic nervous system (ANS) and its role in homeostasis, states of defense including hypervigilance and threat reactions, and affiliative social behavior.

2 | THE POLYVAGAL THEORY

The ANS is a network of afferent and efferent neural pathways that regulates homeostatic and defensive functions, contributes to affective states, influence social behavior, and controls digestive processes. While homeostatic regulation is crucial for maintenance of the brain and body, organisms have a range of possible steady states, which may shift based on internal and external needs (Bernard, 1865; Langley, 1921; Cannon, 1929; Hess, 1948; Jänig, 2006). Such state regulation is critical for organism survival in response to internal (e.g., ingested toxins) and external (e.g., risk of bodily harm) safety and danger cues.

As described in the Polyvagal Theory, the structural organization and function of the human ANS is rooted in its phylogenetic heritage (Porges, 1995, 2001, 2007). Early vertebrate autonomic systems, such as those of jawless and cartilaginous fish, promoted behavioral shut down in response to threats by reducing metabolic functions. With time, these shut down systems were joined by fight/flight systems for mobilization in response to threats. Our phylogenetically newest autonomic system emerged with the transition from primitive reptiles to mammals. This system, building on the architecture of its predecessors, functionally dampened threat responses and promoted the affiliative, social behaviors crucial for mammalian life. Though new systems have emerged over the course of evolution, these built on the existing structures of older systems. In humans, these systems are the ventral vagal complex (VVC), the sympathetic nervous system (SNS), and the dorsal vagal complex (DVC; see Figure 1). As the integration of the VVC, SNS, and DVC circuits in the brainstem evolved, ingestive and digestive functions became vulnerable to cues of threat and maintained by cues of safety. Though functionally these systems are involved in homeostatic and threat responses, their response hierarchy and innervation patterns provide an understanding of the link between the brain and the GI tract, and the developmental mechanisms that give rise to their dysfunction.

The VVC is the phylogenetically youngest, most rapidly acting (due to its myelination), and least homeostatically disruptive challenge-response system. The VVC evolved during transition from primitive reptiles to mammals. Its motor pathways provide innervation for structures above the diaphragm. These motor pathways are visceromotor (i.e., regulators of the smooth muscles of visceral organs) and somatomotor (i.e., regulators of striated muscles). The visceromotor pathways emerging from the VVC include myelinated vagal fibers originating in the nucleus ambiguus and innervating the heart, upper esophagus, and bronchi. The somatomotor pathways emerging from the VVC include the special visceral efferent fibers traveling via five cranial nerves (i.e., trigeminal, facial, glossopharyngeal, vagus, and accessory) that innervate the striated muscles of the face and head. These are involved in supradiaphragmatic digestive functions such as sucking, swallowing, and mastication. The VVC links these functions with autonomic state regulation and affiliative social functions (e.g., facial, head turning and middle-ear muscles that aid the extraction of social

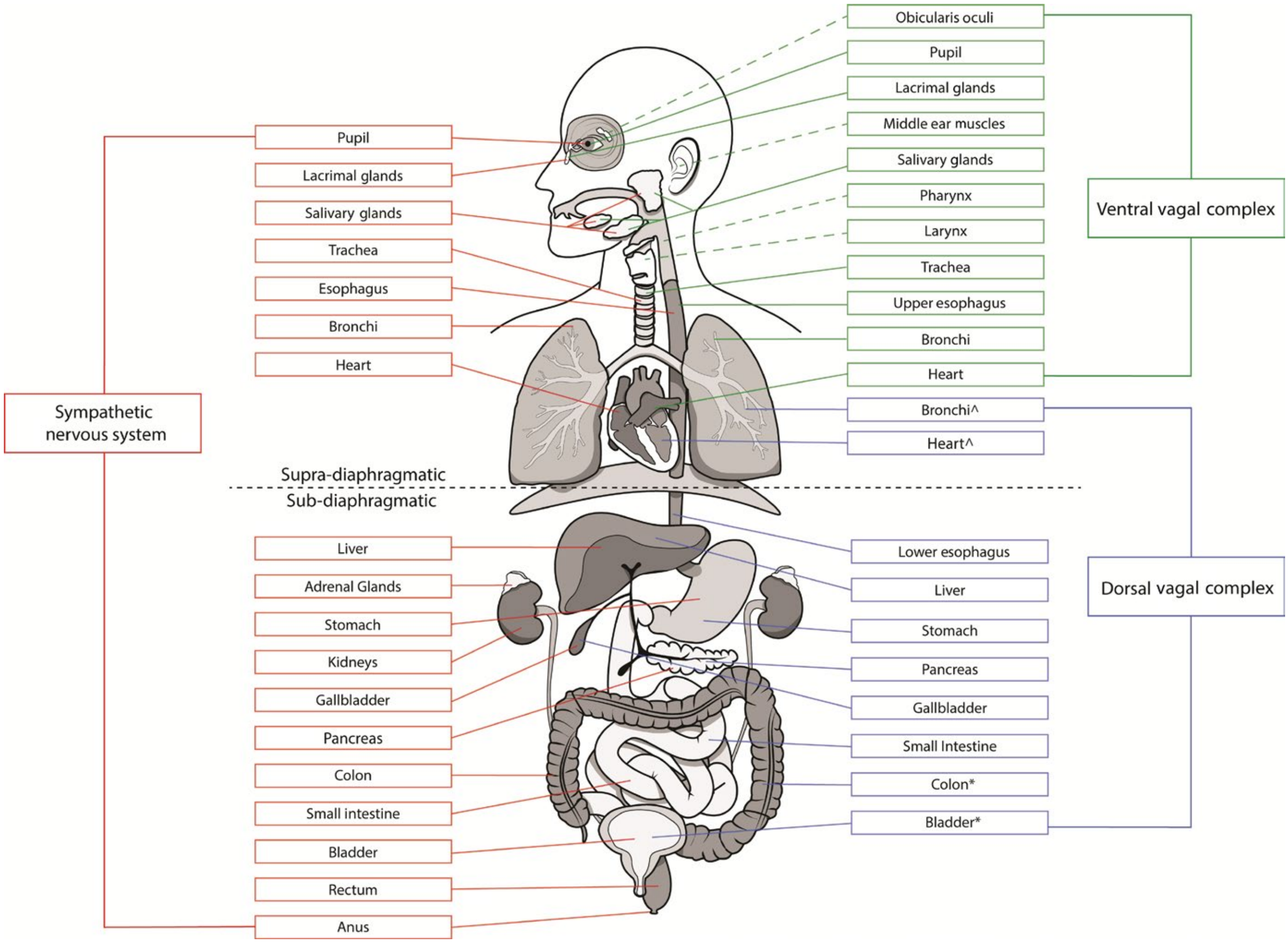

FIGURE 1 Afferent–efferent brain-body connections formed by the ventral vagal complex (VVC), dorsal vagal complex (DVC), and the sympathetic nervous system (SNS), as described by the Polyvagal Theory. In the VVC, solid lines represent a visceromotor component (myelinated vagal pathways) and dashed lines represent somatomotor components (special visceral efferent pathways that regulate the striated muscles of the face and head). Both the DVC and SNS interact with the enteric nervous system. Key: *Afferent pathways only, ^as proposed by the Polyvagal Theory. *Source*: Figure by Olivia K. Roath and Jacek Kolacz, incorporating elements from works by Erin Silversmith (https://commons.wikimedia.org/wiki/File:Tear_system.svg CC 2.5), Patrick J. Lynch (https://commons.wikimedia.org/wiki/File:Heart_circulation_diagram.svg CC 2.5, https://commons.wikimedia.org/wiki/File:Lungs_diagram_detailed.svg CC 2.5), Olek Remesz (https://commons.wikimedia.org/wiki/File:Tractus_intestinalis_esophagus.svg; CC 2.5), and Mariana Ruiz Villarreal (https://commons.wikimedia.org/wiki/File:Digestive_system_simplified.svg; Public domain) used in accordance with the Creative Commons 2.5 generic license (CC BY 2.5; https://creativecommons.org/licenses/by/2.5/deed.en)

acoustic signals from noise, predator calls, and distress cries) to form a Social Engagement System. Under typical conditions, the VVC slows the heart, promotes safety-related affiliative states, and inhibits the threat-related functions of the SNS and DVC. The cardiac vagal pathway functions as a brake, facilitated by the cardioinhibitory neurons emerging from the nucleus ambiguus, and has a respiratory rhythm (Hering, 1910). Its function can be indexed noninvasively by the amplitude of respiratory sinus arrhythmia (also called high frequency heart rate variability; Berntson et al., 1997). In response to threat, the active slowing effect is lifted and a rapid, graded metabolic increase takes place. However, due to its lack of innervation of structures below the diaphragm, functional withdrawal of the VVC does not directly influence the function of the gut. Thus, this response system is the least metabolically disruptive and could be conceptualized as protecting the homeostatic regulation of the gut via the SNS and DVC.

The SNS efferent outflow originates from the thoracic and upper lumbar spinal segments, promoting homeostatic functions and fight–flight threat responses. It innervates the salivary and digestive glands, esophagus, stomach, liver, gallbladder, pancreas, large and small intestines, rectum, the sphincters of the GI tract, blood vessels, adipose tissue, multiple immune function organs (lymphatic tissues, including those of the GI tract), and forms connections with the enteric nervous system (producing largely indirect effects on gut motility and secretion). The SNS exerts inhibitory influences on intestinal secretomotor function via enteric nerve plexuses and smooth muscle with sympathetic input from thoracic spinal cord via cholinergic neurons that control postganglionic adrenergic neurons in the celiac ganglion (Roman & Gonella, 1987; Sato, 1997). In addition to digestive structures, it also innervates organs controlling homeostatic and threat-response functions, including the heart, bronchi, lungs, sweat glands, and blood pressure control regulators. The SNS is phylogenetically older than the VVC. Most of its postganglionic axons are unmyelinated (Jänig, 2006) and thus conduct action potentials at slower, less efficient rate than the VVC. While its activation promotes faster heart rate and respiration, it has many metabolic effects throughout the body due to its many visceral targets in the gut. The action of this system promotes mobilization for active threat responses such as escape or confrontational defense.

The DVC is involved in both homeostatic and threat reactions. The DVC primarily innervates organs below the diaphragm. The tight coupling between this system and digestive functions is exemplified in the name “pneumogastric nerve” used to refer to the vagus nerve in the 19th century. As described in the Polyvagal Theory, the DVC is the phylogenetically oldest of the autonomic subsystems and includes a vestigial immobilization function that first arose in early vertebrates. It is a visceral sensorimotor circuit composed of vagal afferents, second-order neurons of the nucleus of the solitary tract (NTS), and efferent pathways emerging from the dorsal motor nucleus of the vagus (DMNX). It coordinates digestive functions across broad regions via direct gut innervation and interactions with the enteric nervous system - across the lower esophageal sphincter, stomach, liver, gallbladder, pancreas, and small intestine. It supplies control signals via an excitatory pathway (increasing gastric tone, motility, and secretion through activation of muscarinic cholinergic receptors) and a nonadrenergic, noncholinergic inhibitory pathway that reduces gastric functions mainly via release of nitric oxide or vasoactive intestinal polypeptide (Goyal, Guo, & Mashimo, 2019; Travagli, Hermann, Browning, & Rogers, 2006). The DVC is closely involved in regulating stomach secretions, fundic tone, motility, and emptying; without this active regulation, the stomach is incapable of performing its routine functions (Rogers and Hermann, 2012). The DVC also affects functions of the intestine and defecation. In general, DVC actions operate via feedback loops wherein efferent signals to the GI tract sent from DMNX are regulated by afferent signals via NTS, which has a viscerotopic organization. These vagal afferent pathways also likely integrate signals from the colon and bladder (Herrity, Rau, Petruska, Stirling, & Hubscher, 2014). The dysfunction of this subsystem may result in delayed gastric emptying and intestinal dysmotility that may promote abdominal pain, early satiety, bloating, nausea, vomiting as well as defecation problems. As proposed by the Polyvagal Theory, this system disrupts digestive processes and conserves metabolic resources when recruited during threat responses. It also innervates the heart and bronchi, assisting with their regulation.

These ANS component subsystems all contribute to homeostatic functions. However, their function is controlled moment-to-moment by processes of safety and threat detection. These detection systems operate largely outside of conscious awareness, via neuroception (in contrast to the conscious awareness of sensory perception; Porges, 2004). Neuroception integrates internal and external safety and danger signals and coordinates somatic, affective, and autonomic responses that rely on descending information from higher brain regions and ascending information from the body. Afferent pathways from thoracic, abdominal, and pelvic cavities encode physical and chemical events, conveying interoceptive information from the GI tract, which shapes visceral sensations (including discomfort and pain), emotions related to these sensations, and sickness behavior. Environmental events are encoded via exteroceptive systems. The Polyvagal Theory proposes that under typical conditions, autonomic and behavioral responses to threats occur in a response hierarchy, where the phylogenetically youngest, most metabolically efficient subsystems are recruited first. If younger systems and the behaviors they promote are unsuccessful in eliminating danger, phylogenetically older, more homeostatically disruptive functions come online. Safety-related states promote social interactions, affiliative co-regulation, ingestion, and a calm physiological state that facilitates digestion while threat-related states trigger defensive strategies that disrupt ingestion and digestion, social engagement behaviors, and feelings of safety. As a result of the brain-gut pathways that regulate autonomic functions, homeostatic disruptions may manifest in GI tract dysregulation, adversely affecting GI tract sensation, motor function, and secretions.

3 | AUTONOMIC REGULATION LINKS PSYCHIATRIC PROBLEMS AND GI DYSFUNCTION: EMPIRICAL EVIDENCE

Autonomic state regulation provides a plausible linking factor for the comorbidity between psychosocial and GI dysfunction. Problems in both domains are linked through heightened threat-responses and dampening of normal homeostatic brain-body feedback loops that integrate information from brain regions such as the amygdala, the periaqueductal grey, and the hypothalamus (see Jänig, 2006; LeDoux, 2000) as well as ascending information from the body (e.g., Craig, 2003, 2015; Thayer & Lane, 2009; Critchley & Harrison, 2013). Observation studies show that both psychiatric dysfunctions and GI problems are linked with elevated threat-responsive autonomic regulation and difficulty with recovery after challenges. VVC activity (indexed by high frequency heart rate variability; HF-HRV) is depressed or less flexibly regulated in patients with IBS (Liu, Wang, Yan, & Chen, 2013; Mazurak, Seredyuk, Sauer, Teufel, & Enck, 2012), functional nausea and vomiting disorders (Tarbell et al., 2014; To, Issenman, & Kamath, 1999), major depressive disorder (Schiweck, Piette, Berckmans, Claes, & Vrieze, 2019), and a range of anxiety disorders (Chalmers, Quintana, Abbott, & Kemp, 2014).

Animal studies provide evidence that the brain-gut autonomic feedback loops are highly sensitive to modulation from higher level structures such as the medullary raphe nulcei (involved in affective regulation), the amygdala (involved in fear and emotional arousal), and the hypothalamus (involved in a range of state regulation functions). For instance, thyrotropin releasing hormone (in interaction with serotonin) from the raphe obscurus and pallidus of the medullary raphe nuclei can induce dysregulated gastric motility and secretion by activating DMNX cholinergic projections while inhibiting NTS activity (McCann, Hermann, & Rogers, 1989; Rogers & McCann, 1989). The effect is an increase in GI activity without the typical afferent feedback needed for regulation and accelerated intestinal transit (Zhang, Wang, & Zhang, 2018). The hypothalamic-pituitary-adrenal axis has a well-characterized role in perturbation of homeostasis and stress-induced GI symptoms as well as gut inflammation (Bonaz, Sinninger, & Pellissier, 2016; Chrousus, 1995; la Fleur, Wick, Idumalla, Grady, & Bhargava, 2005; Mayer, 2011). Preclinical studies support the role of corticotrophin releasing factor (CRF) signaling affecting gastric acid secretion, gastric and small intestinal transit, mucosal permeability, and visceral hypersensitivity via ANS effects (Tache, Larauche, Yuan, & Million, 2018). Centrally injected CRF causes disturbed GI secretomotor function and anxiety-like behaviors in animals and reversal of this has been documented using CRF antagonists (Martinez & Taché, 2006; Tache et al., 2018). In addition, oxytocinergic projections from the paraventricular nucleus (PVN; located in the hypothalamus) to the DVC increase the sensitivity of vagovagal reflex and serve a protective role in maintaining GI functions during restraint stress (Bülbül, Babygirija, Ludwig, & Takahashi, 2010; Rogers & Hermann, 1985, 1987; 2012). PVN lesions sharply diminish the sensitivity of brainstem vagovagal reflexes in response to afferent stimulation, highlighting its importance to responding to internal events. Threat-responsive VVC withdrawal may also be implicated in afferent and efferent dysfunction related to GI function including swallowing disorders and chronic throat discomfort without an identifiable physical cause (globus pharyngeus; Grooten-Bresser, Kolacz, Kooijman, Chenault, & Holmes, in preparation). These regulatory functions of higher-level integration centers provide a mechanism for promoting safety- and danger-related changes in ANS and suggest a substrate for long-term ANS changes after traumatic stress.

4 | TRAUMA AND AUTONOMIC FUNCTION: EMPIRICAL EVIDENCE

Trauma survivors often report difficulty controlling their autonomic functions, with threat-related psychological difficulties such as hyper-vigilance for danger and overwhelming anxiety or anger (van der Kolk et al., 2014). PTSD is associated with dampened HF-HRV (Chalmers et al., 2014), suggesting poor VVC regulation, in support of chronic threat-related autonomic state. In addition, trauma survivors with PTSD have reduced correspondence between RSA and heart period in response to stressors when compared to those without PTSD, also suggesting that their state regulation is not under VVC control (Sahar, Shalev, & Porges, 2001). However, the PTSD diagnosis is not comprehensive of the many medical and psychiatric problems experienced by trauma survivors. VVC activity is dampened and reactions to stressors are atypical in women with a maltreatment history, even when they do not meet the criteria for PTSD, and is related to higher rates of psychological distress (Dale et al., 2009, 2018). Moreover, trauma survivors are at increased risk of developing somatic problems such as chronic widespread pain and GI problems, which are consistent with shifts in autonomic state regulation (Kolacz & Porges, 2018).

5 | EMERGING EVIDENCE FOR DEVELOPMENTAL PATHWAYS

As described above, the ANS provides a mechanism for maintaining homeostasis and responding to challenges. Developmental processes can shape and alter ANS function throughout the life-span. In many cases of traumatic stress, threat response states are maintained even after the threat has passed. As outlined in the Polyvagal Theory, state regulation is an integrative process that involves interoception (internal body state), exteroception (external conditions), and feedback loops that alter affect, sensation, and behavior. Following a disruption, threat-responsive states may become self-perpetuating via their own systemic momentum and feedback loops. At the teleological level, this type of long-term state shift allows an organism to "sample" safety and threat during development and make long-term adjustments that optimize its function for a specific environment. Some of these effects, such as hypervigilance and sensitized threat responses, are indicative of the adaptive calibration for survival in dangerous environments. Other outcomes such as chronic abdominal pain do not have obvious adaptive value and, we argue, are caused by disruption of the feedback loops necessary for optimal function (see also Kolacz & Porges, 2018). We describe here several potential mechanisms for promoting and maintaining ANS threat activation.

Internal afferent–efferent feedback loops may maintain or exacerbate threat response states. Changes induced by threat responses may trigger afferent signals that contribute to further threat-response state shifts and their maintenance. These effects are supported by animal studies indicating that maintained autonomic responses may be partly based on the interactions with immune function and microbiota (Mayer, Labus, Tillisch, Cole, & Baldi, 2015). The ANS via its parasympathetic branch is a central mediator of the microbiota-gut-brain axis, dysfunction of which is thought to underlie both functional and inflammatory GI disorders (Bonaz, Bazin, & Pellissier, 2018). GI inflammation has been linked to negative emotional states and autonomic reactivity in both animal models and human studies (Bonaz et al., 2016; Cielsielczyk, Furgała, Dobrek, Jusczak, & Thor, 2017; Ghia et al., 2009). Vagally mediated anti-inflammatory action is demonstrated in animal models of inflammatory bowel disease and depressive-like behaviors are linked to increased inflammation via vagal nerve pathways (Ghia, Blennerhassett, & Collins, 2008; Ghia et al., 2009; Ghia, Blennerhassett, Kumar-Ondiveeran, Verdu, & Collins, 2006). A vagal anti-inflammatory reflex termed the cholinergic anti-inflammatory pathway has been described in a model of acute inflammation (Bonaz, 2007; Borovikova, Ivanova, Nardi et al., 2000; Borovikova, Ivanova, Zhang et al., 2000). Vagal nerve afferent fibers distributed throughout all layers of the GI tract communicate with the brain via signaling with enteroendocrine cells, releasing a variety of neurotransmitters and gut hormones. Reduced cardiac vagal tone has been demonstrated not only in IBS but also in patients with inflammatory bowel disease (Pellissier, Dantzer, Canini, Mathier, & Bonaz, 2010; Pellissier et al., 2014) and may be an avenue for novel therapeutic interventions. Inflammatory bowel diseases such as Crohn's disease or ulcerative colitis often co-occur with anxiety and depression (Graff, Walker, & Bernstein, 2009; Mayer, 2011). Although stress is a potential trigger of inflammatory bowel disease (Sartor, 2006), more studies are needed to examine whether traumatic experiences may contribute to their pathogenesis.

Some threat state maintenance may be due to heightened sensitivity to sensory threat cues, which increase the salience of danger triggers in the environment. Sensitization of facial anger cues is enhanced in children with a history of physical abuse (e.g., Pollak & Tolley-Schell, 2003) and those who survived the Sierra Leonean Ebola virus outbreak (Ardizzi et al., 2017). There is evidence of auditory changes promoting threat response sensitivity as well. VVC regulation of the middle ear muscles may influence the salience of high and low frequency sounds (evolutionary cues of conspecific distress and predator calls, respectively), maintaining autonomic threat responses via perpetuation of threat-type signals at the cost of frequencies signaling safety (Kolacz, Lewis, & Porges, 2018; Porges & Lewis, 2010). There is increasing evidence that auditory hypersensitivities are elevated in PTSD, anxiety, and depression (Beutel et al., 2016; Jüris, Andersson, Larsen, & Ekselius, 2013; Paulin, Andersson, & Nordin, 2016). Additional studies are needed to understand the link between auditory hypersensitivities and psychosocial problems.

Another developmental pathway of threat-state maintenance may be due to interpersonal interactions wherein individuals reflect and regulate one another's states and contribute to ongoing state organization. Studies from child development suggest that state regulation is an important contributor to interpersonal dynamics over time. For instance, longitudinal data demonstrate that children's resting VVC control predicts more supportive and less restrictive parenting in early childhood (Kennedy, Rubin, Hastings, & Maisel, 2004) and that maternal sensitivity predicts children's flexible VVC control in response to frustration, which—in turn—predicts higher maternal sensitivity (Perry, Mackler, Calkins, & Keane, 2014). These observations may reflect evocative effects, wherein heightened autonomic mobilization is expressed in behavior cues, voice, and facial affect, which promote feedback loops with caregivers, significant others, and other interaction partners. Thus, autonomic regulation may be a part of the cascading cycle of individual-environment interactions that may cause and maintain state regulation problems over time. Oxytocin and oxytocin receptor signaling, which is involved in social regulation and safety processes in interaction with the ANS (Carter, 2014) also plays a role in GI functions in the gut and likely has direct effects on the epithelium and enteric neurons, affecting inflammation, motility, and gut permeability (Welch & Ludwig, 2017; Welch, Margolis, Li, & Gershon, 2014). However, studies are needed to directly test whether these interactive effects with autonomic state regulation are part of the brain-gut axis problems evidenced after trauma.

The ANS is regulated in coordination with cognition and behavior, guiding affiliative social engagement or promoting impulsive aggression and risk taking (Bechara, Damasio, & Damasio, 2000; Critchley & Harrison, 2013). Behavioral changes also likely play a role in maintaining threat responses, reflecting a niche construction effect of mutually enforcing ANS-mobilizing events and responses. As reviewed above, more threat-reactive autonomic regulation (i.e., dampened VVC control) is common among trauma survivors. Though direct empirical evidence is lacking, some longitudinal evidence points to interpersonal and decision-making problems related to PTSD as assisting in maintaining symptomology. Military veterans who experience potentially traumatic events have elevated rates of risky and self-destructive behavior, which predict new adverse events and subsequent increase in PTSD severity (Lusk, Sadeh, Wolf, & Miller, 2017; Maniates, Stoop, Miller, Halberstadt, & Wolf, 2018; Sadeh, Miller, Wolf, & Harkness, 2015). A similar effect was observed in a longitudinal study of responders to the September 11, 2001 World Trade Center terrorist attack in New York City, wherein PTSD and depression after the attack predicted stressful life occurrences (interpersonal and financial problems), which in turn predicted PTSD and depression severity (Zvolensky et al., 2015). Though tentative, these studies point to the need for longitudinal data addressing the role of state regulation on decision-making and their potential mutually supportive effects.

Functional GI symptoms fluctuate with emotional states and life challenges (Blanchard et al., 2008; Dancey, Taghavi, & Fox, 1998). As reviewed above, these fluctuations likely reflect changes in autonomic state that give rise to changes in physical functioning (such as disruption of gut-brain feedback loops that maintain homeostasis) while also promoting the psychological awareness of the brain-body toward threat response (awareness of emotional stress). The sensory, behavioral, interpersonal, and physiological mechanisms of maintaining and promoting state regulation thus may all contribute to fluctuations in GI function and sensation as well as affective and cognitive experience.

In sum, state regulation effects on individuals' sensory experience, interpersonal function, decision-making (and its impact on niche construction), and physiological feedback loops all provide potential constraints that maintain and amplify GI and psychological function (Figure 2). However, they also offer an opportunity for accessing the plasticity of autonomic state regulation. Understanding these developmental mechanisms opens new intervention targets to promote healthy brain-gut axis regulation.

6 | AN AUTONOMIC STATE REGULATION PERSPECTIVE ON TREATMENT AND PREVENTION OF PSYCHOLOGICAL AND GUT PROBLEMS

Given the associations between affective states and GI dysfunction, functional GI disorders are often attributed to pure psychiatric pathology. This negatively affects patient–physician relationships and

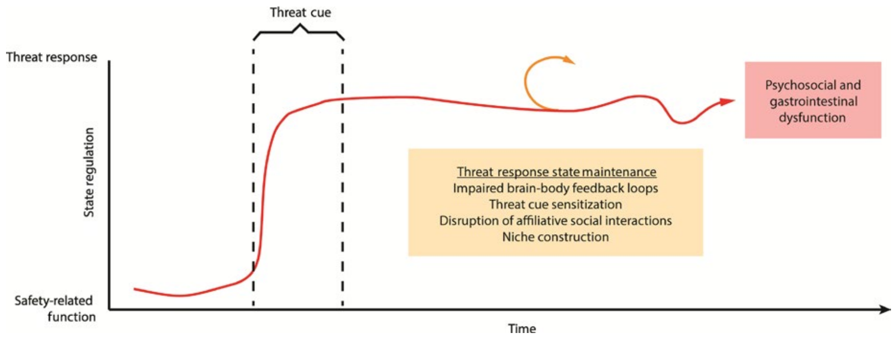

FIGURE 2 Conceptual model for state regulation response to a potentially traumatic event. An autonomic threat response can be facilitated by ventral vagal complex (VVC) withdrawal, sympathetic activation, dorsal vagal complex activation, or their combination. Prolonged threat activation disrupts psychosocial and gastrointestinal function and may be maintained by impaired brain-body feedback loops, threat cue sensitization, disruption of affiliative social interactions that stimulate safety-related systems, and adverse niche construction

complicates management. It leads to stigma surrounding the use of empiric psychotropic drug therapy, even if these may effectively impact the neural circuitry involved (Drossman et al., 2018; Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009). Clarifying the homeostatic role that gut regulation and emotion plays in threat responses, their coordination and their re-tuning after trauma can inform therapeutic approaches and assist clients in understanding their experience. Promising methods for improving state regulation include direct ANS stimulation, ANS-informed neurofeedback, hypnotherapy, cognitive behavioral therapy, yoga, and psychosocial interventions that capitalize on co-regulation of autonomic function.

6.1 | Direct ANS stimulation and ANS-informed neurofeedback

Neuromodulation therapies for GI and psychological pathologies are emerging. These include non- or minimally-invasive stimulation of afferent parasympathetic nerve fibers that innervate the outer ear and project to brainstem NTS (He et al., 2012; Li & Wang, 2012; Mercante, Deriu, & Rangon, 2018; Peuker & Filler, 2002). In adolescents with functional abdominal pain disorders, a large placebo-controlled trial demonstrated improvement in pain and functioning using a novel auricular percutaneous electrical nerve field stimulator (Kovacic et al., 2017). Effects on ANS circuits and GI function are also documented in healthy participants, where transcutaneous electrical vagal nerve stimulation coupled with slow deep breathing increased gastroduodenal motility and HRV (Frøkjaer et al., 2016), and animal models, where VNS has been shown to promote gastric emptying (Lu et al., 2018). Studies also show that vagus nerve stimulation may have positive effects on psychiatric function, strengthening VVC regulation while lessening emotional hyperarousal in individuals with PTSD and traumatic brain injury (Lamb, Porges, Lewis, & Williamson, 2017), improving depression symptoms (Ben-Menachem, Revesz, Simon, & Silberstein, 2015), and reducing anxiety (George et al., 2008). Emerging data also supports direct vagal nerve stimulation as improving inflammatory bowel disease (Bonaz, Sinniger, & Pellissier, 2017; Bonaz et al., 2016). Though the application of direct, low- or noninvasive ANS stimulation is still in early stages, these studies provide support for the autonomic regulation as a promising therapeutic target for problems of the brain-gut axis.

HRV biofeedback via diaphragmatic breathing has also shown efficacy for functional GI disorders (Sowder, Gevirtz, Shapiro, & Ebert, 2010; Stern, Guiles, & Gevirtz, 2014). Multiple studies also show that biofeedback and mindfulness training reduce stress, anxiety, and PTSD symptoms while improving autonomic function (Bhatnagar et al., 2013; Goessl, Curtiss, & Hofmann, 2017; Tan, Dao, Farmer, Sutherland, & Gevirtz, 2011; Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). These data suggest that autonomically informed interventions can modulate the afferent brain processing of stress and emotional responses to gut signals, altering efferent ANS output and visceral sensation.

The efficacy of ANS-based treatments for improving GI symptoms and anxiety, while concurrently increasing VVC function (as measured by RSA), supports a model of autonomic state regulation promoting both psychiatric and functional GI problems. It also provides a promising opportunity for an entry point into the developmental system for treating pathology (reviewed above) or promoting resilience to future disruptions (e.g., HRV feedback training; Lewis et al., 2015). However, the use of ANS-targeted interventions is still a nascent field and many open questions remain about implementation, including optimal parameterization in direct afferent stimulation studies (frequency, amplitude, etc.).

6.2 | Cognitive behavioral therapy

Systematic reviews demonstrate higher efficacy of nonpharmacological interventions such as cognitive behavioral therapy (CBT) compared with current pharmacological therapies in children with functional GI disorders (Korterink, Rutten, Venmans, Benninga, & Tabbers, 2015; Rutten, Korterink, Venmans, Benninga, & Tabbers, 2015). CBT is based on reversing maladaptive thoughts, behaviors, and emotions that result from ongoing hypervigilance, thereby affecting the altered gut sensation and changing behaviors (Levy et al., 2006). As proof of concept, a study showed significant increase in high frequency HRV with concurrent decrease in GI symptoms, anxiety and stress in constipation-predominant IBS after 8 weeks of CBT (Jang, Hwang, Padhye, & Meininger, 2017).

6.3 | Hypnotherapy

Hypnotherapy involves relaxation, suggestions of increased confidence and well-being, as well as techniques aimed at controlling GI dysfunction (Gulewitsch & Schlarb, 2017). It can affect the state regulation by influencing emotional states (Houghton, Calvert, Jackson, Cooper, & Whorwell, 2002; Prior, Colgan, & Whorwell, 1990; Whorwell, Houghton, Taylor, & Maxton, 1992). Many studies in both adults and children demonstrate the efficacy of hypnotherapy for functional GI disorders (Moser et al., 2013; Palsson, Turner, Johnson, Burnett, & Whitehead, 2002; Rutten et al., 2017; van Tilburg et al., 2009; Vlieger, Rutten, Govers, Frankenhuis, & Benninga, 2012). There is a notable concurrent improvement in psychological comorbidities including anxiety, depression, and somatization (Palsson et al., 2002). Furthermore, effects of these interventions are often long-lasting, presumably due to reductions in emotional arousal linked to the GI sensation and alterations in visceral hypersensitivity (Lea et al., 2003; Moser et al., 2013; Palsson et al., 2002).

6.4 | Therapies utilizing tactile, vocal, and interoceptive modalities

Several studies support exteroceptive and interoceptive modalities as promising targets for altering autonomic state regulation to improve GI and psychosocial problems. There is substantial evidence that therapy targeting psychosocial factors most effectively improves outcomes in functional GI disorders (Levy et al., 2006; Windgassen et al., 2017). This includes a thorough assessment of psychosocial factors followed by psychological therapies such as relaxation training, dynamic psychotherapy, yoga, or a combination of these (Levy et al., 2006; Paul & Basude, 2016). The practice of yoga, with emphases on interoceptive and exteroceptive sensory-motor experience, has an intimate link with autonomic state regulation (Sullivan et al., 2018). There is growing evidence that yoga reduces PTSD symptoms (van der Kolk et al., 2014; Price et al., 2017) and may have benefits for treating functional GI disorders in adolescents and adults (for a systematic review see Schumann et al., 2016).

Evidence suggests that perinatal problems, such as preterm or very low birth weight delivery, increase the probability of IBS and psychiatric disorders later in life (Bengtson, Rønning, Vatn, & Harris, 2006; Nosarti et al., 2012), pointing to the need for early intervention prior to disorder manifestation. Perinatal autonomic regulation is a particular challenge because the VVC develops relatively late in utero (Porges & Furman, 2011; Suess et al., 2000). This places children at risk for being born with a tenuously functioning VVC, especially if they are born preterm. Preterm birth is associated with ingestion problems, including ineffective sucking and swallowing and feeding disorders. Skin-to-skin contact (Kangaroo Care), which promotes tactile state co-regulation between mother and infant, has shown improvements in autonomic state regulation and faster maturation of neurodevelopmental profiles in preterm infants (Feldman & Eidelman, 2003) as well as improvements in breastfeeding (Moore, Anderson, Bergman, & Dowswell, 2012). Children who receive this intervention also exhibit higher cardiac VVC regulation (measured by RSA), attenuated stress response, better cognitive control, and better organized sleep through the first 10 years of life (Feldman, Rosenthal, & Eidelman, 2014). The Family Nurture Intervention, a psychosocial intervention based on Calming Cycle Theory that promotes mother-infant emotional connection through direct interpersonal communication of affect (Welch, 2016) has also shown promise in preterm infants, with benefits for VVC regulation, socioemotional function, and neurodevelopmental outcomes (Porges et al., in press; Welch et al., 2015). Interventions focused on parent–child interactions may also improve autonomic function in older children (e.g., Hastings et al., 2019). In sum, these interventions support social autonomic state regulation as a treatment target.

7 | CONCLUSION

Based on the Polyvagal Theory, we have proposed a model of comorbid socioemotional and GI dysfunction as arising from phylogenetically informed chronic threat responses, which alter sensory-motor processes and homeostatic feedback loops throughout the body. We have also outlined probable, though nonexhaustive, developmental mechanisms that may promote and maintain threat-response states even after the triggering threat has subsided.

In addition to the mechanisms outlined here, genotypes may confer risk or resilience for psychosocial and GI disturbance through their effects on autonomic function. Genotypes may interact with environmental stressors and sources of support to contribute to a range of individual developmental trajectories (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011; Del Giudice, Ellis, & Shirtcliff, 2011). There is also growing evidence from animal models that stress or trauma may affect offspring through epigenetic mechanisms (Yehuda & Lehrner, 2018) and research is also needed to examine these effects in humans and their relation to autonomic state regulation.

The preliminary empirical evidence for state regulation feedback loops and the currently available evidence for treatment approaches that directly or indirectly affect autonomic state regulation are encouraging. However, there is a need for more prospective longitudinal data that can further test the proposed model and expand the empirical evidence around threat-response mechanisms over time. Studies that prospectively examine traumatic experiences are particularly scant. Longitudinal data and more research into autonomically targeted treatments, informed by an understanding of sensory-motor processes that are sensitive to threat and safety cues, can help identify the most promising entry points into the autonomic-environmental manifold for understanding factors that confer risk and resilience, prevent dysfunction, and optimize treatment.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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