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CRANIOSACRAL THERAPY AND THE PATHOPHYSIOLOGY OF THE CRANIOSACRAL SYSTEM: MECHANISMS, CONTROVERSIES, AND PROPOSED FUTURE RESEARCH DIRECTIONS

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Craniosacral therapy (CST) is a non-invasive, alternative therapeutic approach based on the concept of the craniosacral system and its inherent rhythm. This rhythm is a subtle, cyclical expansion and contraction of the dural membranes and cerebrospinal fluid (CSF), which regulates intracranial pressure and the physiological function of the craniosacral system (CS). The CS constitutes a semi-closed, physiological hydraulic network comprising the skull (cranium), the sacrum (tailbone), the associated membranes, and the circulating CSF. Within this system, CSF provides both protection and nourishment to the brain and spinal cord – the body's most vital organs. The craniosacral rhythm (CSR) refers to the physiological rhythm of expansion and contraction within the CS that regulates CSF pressure. Magnetic resonance imaging (MRI) studies have demonstrated the pulsatile nature of intracranial and spinal CSF circulation of approximately 6 to 12 cycles per minute. Experienced CST practitioners palpate this rhythm and assess it for abnormalities that may indicate dysfunction in the fascia, dural membranes, or CSF flow. CST techniques involve gentle manual palpation to release restrictions in dural and fascial structures and restore homeostasis. Some studies suggest that CST may provide therapeutic benefits for a range of conditions, including migraine headaches, non-specific low back pain, depression, anxiety, fibromyalgia, chronic pain, and improved overall quality of life. However, its efficacy for many other conditions remains controversial, and the scientific evidence supporting its physiological mechanisms is limited. This review presents a balanced overview of CST, highlighting its current clinical status, established and hypothesized mechanisms, and emerging directions for future research into both CST and the underlying pathophysiology of the craniosacral system. Notably, recent high-quality basic research has begun to elucidate potential neurophysiological pathways and pathophysiology relevant to CS. For example, new studies have revealed direct anatomical and functional connections between the dura mater and the brain. Furthermore, they demonstrated that in migraine models, trigeminal ganglion neurons are directly activated by CSF influx. Meningeal lymphatic calcitonin gene-related peptide (CGRP) signaling has been implicated in pain induction through CSF efflux and neuroinflammation. These findings opened new avenues for understanding the physiological underpinnings of CST and its potential impact on neural and autonomic regulation.

Key words: *craniosacral rhythm, craniosacral system, craniosacral therapy, cerebrospinal fluid, central nervous system, dura mater, arachnoid, blood-brain barrier, calcitonin gene-related peptide, glymphatic pathway, magnetic resonance imaging*

INTRODUCTION

The craniosacral system is a physiological concept that refers to the membranes and cerebrospinal fluid (CSF) that surround and protect the brain and spinal cord. It includes: the cranium (skull), the spine, the meninges (dura mater, arachnoid mater, pia mater) and CSF (1-6). This integrated physiological system surrounds and protects the central nervous system (CNS) and plays a crucial role in the functioning of the autonomic nervous system. It primarily interacts with the parasympathetic system to help regulate the body's rest-and-digest or feed-and-breed activities. The autonomic nervous system is the part of the nervous system that controls involuntary actions of muscles and glands, heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. The meninges form a three-layered membrane system – dura mater, arachnoid mater, and pia mater – that encloses the brain and spinal cord and extends from the cranial cavity to the sacral region. The dura mater, the tough outermost layer, consists of an outer endosteal (periosteal) layer attached to the skull and an inner meningeal layer that form dural folds and venous sinuses, facilitating the drainage of blood and CSF (7-10). Cerebrospinal fluid (CSF) is a clear, colorless fluid that circulates within the subarachnoid space, serving as a cushion for the brain and spinal cord, removing metabolic waste products, and maintaining intracranial pressure. CSF production, circulation, and reabsorption create subtle rhythmic pressure fluctuations within the craniosacral system,

leading to slight cyclical expansions and contractions that underlie the craniosacral rhythm. CSF is produced by the choroid plexus within the brain ventricles and circulates through the ventricular system into the subarachnoid space, where it is reabsorbed into the venous circulation and cervical lymphatic pathways (11-17).

In the Greitz *et al*. study, CSF flow was assessed in 24 healthy volunteers using gated MR phase imaging (15). The subarachnoid space was divided into five compartments, depending on the magnitude of the pulsatile CSF flows: a high-velocity compartment in the area of the brainstem and spinal cord, two slow compartments at the upper and lower extremes of the SAS, and finally, two intermediate-velocity compartments in between. The extra ventricular CSF-circulation can be explained by pulsatile CSF flow without the existence of a net flow. A successive time offset has been identified in the fronto-occipital direction during the cardiac cycle, resulting from the interplay among arterial expansion, brain expansion, changes in CSF space volume, and the veins. The authors proposed to name this time offset the intracranial „volume wave“ (VoW).

The neuroimaging studies have provided new insights into CSF dynamics. Dreha-Kulaszewski and coworkers examined how CSF is controlled in humans (18). They applied a novel, real-time magnetic resonance (MRI) technique with high spectral and temporal resolution in healthy subjects. They found a significant CSF flux almost exclusively during inspiration, with only a minor fraction dependent on cardiac pulsation. These studies demonstrated that inspiration is the crucial driving force regulating CSF flow in humans (18).

Furthermore, this experimental approach opened up novel clinical avenues for examining the pathophysiology of hydrocephalus and formulating therapeutic strategies. Dr. Sukrithan commented on this study, calling it a breakthrough that enables real-time measurement of CSF flow without the need for intrathecally injected tracers. The paravascular glymphatic pathway for CSF flow, described by Illif *et al*., facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid (19). This discovery was crucial to understanding neurodegenerative diseases. For example, Alzheimer's disease is associated with an increased size of the perivascular space compared to controls (19), which may be a mechanism (19 - 21) for the removal of misfolded proteins, such as β-amyloid. These findings suggest that essentially all neurodegenerative diseases are associated with misaccumulation of a variety of cellular waste products. Some of these, misfolded or hyperphosphorylated proteins, are among the most challenging for the brain to dispose of. Tau and β-amyloid can accumulate and are neurotoxic in conditions such as Alzheimer's disease. Intracellular proteasomes and autophagy are the primary mechanisms for removing proteins in the central nervous system. The dysfunction of these systems is causally linked to neurodegeneration.

HISTORICAL BACKGROUND OF CRANIOSACRAL THERAPY

The concept underlying CST originated in 1901, when William Garner Sutherland, an osteopathic physician, proposed that the cranial bones are not completely immobile but possess a minute, intrinsic motion (3, 4). He described a "primary respiratory mechanism" involving the cranial bones, dural membranes, and CSF flow. Sutherland hypothesized that restrictions in this mechanism could influence overall physical, emotional, and mental health. In the 1970s, Dr. John E. Upledger, another osteopathic physician, observed rhythmic motion of the spinal membranes during neck surgery and subsequently developed these observations into a therapeutic approach known as craniosacral therapy (6-8, 22). Upledger later founded the Upledger Institute in 1985 to promote clinical education and research in CST, which led to its widespread recognition as a gentle, non-invasive manual therapy.

The most recent update (2025) from the Upledger Institute International noted its collaboration with the Barral Institute, founded by Jean-Pierre Barral, to address functional and structural imbalances in the musculoskeletal, vascular, nervous, urogenital, respiratory, digestive, and lymphatic systems. Together, the institutes focus on CST, visceral manipulation, and neural manipulation, providing support for individuals with brain injuries and post-traumatic stress disorder (PTSD). These two Institutes emphasize a growing need for effective, non-invasive complementary therapies to help military Veterans, first responders, and athletes struggling with mild traumatic brain injuries (MTBI), concussions, neurological challenges, and co-morbid psychological conditions such as post-traumatic stress, depression, and anxiety. Among Veterans, MTBI may result from traumatic events that disrupt normal brain function, while PTSD can place the nervous system in a chronic "freeze" state. This state reduces CSF circulation in the brain, contributing to dysfunction and potential pathological changes. For athletes, repeated sub-concussive impacts may similarly decrease CSF circulation and may also contribute to PTSD-like symptoms due to structural and functional changes within the brain. Reduced CSF flow can predispose individuals to long-term neurological disorders, including blood-brain barrier damage and eventual neural tissue degeneration. Recent communications from the Upledger Institute International and the Barral Institutes highlighted senior leadership contributing to research and international education in manual and integrative health sciences. Thomas Rasmussen, PhD (Medical Science), MSc (Chemistry), serves as Director of Research at the Upledger Institute International, with over 30 years of experience in scientific research and evidence-based medicine related to manual therapy. Dawn Langnes Shear, Chief Development Officer and Co-Chief Executive Officer of the Upledger and Barral Institutes, oversees global development, research initiatives, publishing, and strategic partnerships across more than 70 countries. She also serves on the Integrative Health Policy Consortium. Avadhan Larson, LAc, LMT, CST-D, RCST, SEP, is a Senior Instructor at the Upledger Institute International and a Diplomate Certified Craniosacral Therapist with over 35 years of clinical and teaching experience, providing international instruction in craniosacral therapy, including somatoemotional release. Located in Denver, Colorado USA.

PHYSIOLOGICAL BASIS AND MECHANISMS

CST is based on the concept of a craniosacral rhythm – a subtle, cyclical expansion and contraction within the dural membranes and CSF that occurs approximately 6 to 12 times per minute (8). This rhythm reflects the dynamic balance between CSF production and absorption. The pulsatile nature of intracranial and spinal CSF circulation was demonstrated by MRI (7). The therapy utilizes the palpated rhythm to identify restrictions, imbalances, or blockages within the craniosacral system. Therapists apply gentle, sustained pressure to the cranium and sacrum to release restrictions. The therapy utilizes the palpated rhythm to identify restrictions, imbalances, or blockages within the craniosacral system. The overall goal is to release restrictions, correct imbalances, and facilitate the body's innate healing mechanisms, thereby promoting overall balance and enhanced function. Engagement with the subtle expressions of the craniosacral system is essential to the process.

Craniosacral integration is not a matter of applying techniques on a superficial, mechanical level; it is an interaction between the patient and the therapist. Through engagement, the practitioner will become aware of quality, symmetry, and motion – the individual characteristics of the person, including any imbalances or asymmetries, as well as movement in various forms (vibration, pulsation, rocking, swirling, *etc*.), including rhythmic motion. These are the guiding elements that will enable the practitioner to make a comprehensive diagnosis and facilitate appropriate response and treatment.

HOW IS CRANIOSACRAL THERAPY APPLIED?

The goal of CST is to release restrictions, correct imbalances, and facilitate the body's natural healing mechanisms. Craniosacral integration is not simply the application of mechanical techniques but an interactive process. Through engaged palpation, the practitioner becomes aware of the quality, symmetry, and motion of the craniosacral structures, including any imbalances, asymmetries, or patterns of movement such as vibration, pulsation, or rhythmic motion. These observations guide assessment and treatment. Practitioners evaluate the quality, symmetry, and amplitude of the craniosacral rhythm by palpating subtle tissue movements at the cranial and sacral regions. Gentle, sustained pressure is then applied to release myofascial and dural restrictions that may impede cerebrospinal fluid flow or disrupt craniosacral balance. Through this process, CST aims to reduce tension, enhance physiological function, and support the body's intrinsic self-regulatory mechanisms. Experienced CST therapists use gentle pressure on the cranium and sacrum to release restrictions in the myofascial structures, thereby improving the movement and symmetry of the cranial bones and dural membranes. The therapeutic interaction between the patient and practitioner may generate subtle forms of energy that are currently unmeasurable. Albert Einstein, in a 1954 interview (https://intellectual-enlightenment.com/einsteins-banned-afterlife-interview-45f2e900d5c2?gi=f44fb008e9e3), suggested that consciousness may influence our understanding of reality and has been interpreted by some as acknowledging consciousness as a form of energy. Supporters of CST propose that such energy may help normalize craniosacral rhythms and release tension, thereby balancing the sympathetic and parasympathetic nervous systems and promoting relaxation and improved physiological regulation. "Four-hand" craniosacral therapy involves two practitioners working simultaneously with the patient. This approach is believed to amplify the light-touch modality's ability to detect and release restrictions in the craniosacral system, potentially leading to more profound shifts and improved outcomes through combined focus, attention, and energetic support.

Craniosacral therapy for animals is a gentle, hands-on bodywork method that works with the animal's craniosacral system, which includes the skull, spine, membranes, and cerebrospinal fluid, to promote the body's natural healing process. This light-touch therapy can benefit animals, such as dogs, horses, and cats, by addressing pain, anxiety, digestive issues, trauma, and recovery from injury or surgery. It also improves the flow of cerebrospinal fluid and releases restrictions in the connective tissue (23, 24).

There is a growing expectation that evidence-based medicine should be applied to CST. According to Sackett *et al*., "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (25). The relatively small number of studies published to date on CST provides limited evidence in support of the therapy.

The National Institute of Health (NIH) in the USA does not endorse craniosacral therapy (CST) as a clinically proven treatment, stating that the available evidence is insufficient and often flawed, with systematic reviews concluding there are no statistically significant or clinically relevant benefits for the musculoskeletal or non-musculoskeletal conditions studied, including headache, low back pain, and infant colic. However, it should be noted that a similar statement was issued in the early 1980s regarding the association between *Helicobacter pylori* and peptic ulcer disease. The NIH rigid view had been delayed by more than 10 years (compared to Japan and Europe), and the effective treatment of peptic ulcer with drugs aimed at eradicating *Helicobacter pylori*.

Numerous clinical studies demonstrated the efficacy of CST. They showed that:

– CST, together with balance and coordination exercises, can be a more effective and faster treatment to improve these motor skills, correcting and improving alterations during child neurodevelopment (26).

– Craniosacral therapy is effective and safe for infantile colic, reducing the number of crying hours, colic severity, and increasing total sleep hours (27).

– A 2022 study found that a craniosacral therapy (CST) protocol was effective in improving pain, frequency of migraine episodes, disability, and medication intake in individuals with migraine. The benefits were also maintained at follow-up assessments, suggesting that CST could be a valuable therapeutic approach for managing migraine symptoms (28).

– A protocol based on craniosacral therapy is efficacious in improving pain, frequency of episodes, functional and overall disability, and medication intake in patients with migraine. Therefore, this protocol may be a reasonable alternative therapeutic approach in migraine patients.

– A protocol based on craniosacral therapy is efficacious in improving neck pain, reducing the frequency of episodes, and is specifically effective and safe in reducing neck pain intensity. It may improve functional disability and quality of life for up to 3 months after the intervention (29).

– The study aimed to evaluate the application of CST in individuals diagnosed with post-concussion syndrome demonstrated that a considerable proportion of participants across all cohorts indicated that CST produced beneficial effects on their symptoms (30).

– CST is effective in treating patients with non-specific low back pain (31).

– Preliminary studies suggest that CST may offer benefits in conditions such as migraine, non-specific low back pain, fibromyalgia, and anxiety (32). Patients often report improvements in pain, stress, and overall well-being. However, systematic reviews and meta-analyses have noted methodological limitations in many of these studies, including small sample sizes, lack of blinding, and subjective outcome measures. As a result, the clinical efficacy of CST remains a topic of debate, and its mechanisms of action are yet to be clearly established.

– Vietnam Veterans Study. A two-week intensive therapy program using CST was conducted to address post-war symptoms, including PTSD. Outcomes showed significant improvements: Veterans' obsessive-compulsive scores dropped from the 86*th* percentile to the 46th; depression scores fell from 69 to 27; and anxiety scores declined from 79 to 42.

– A recent narrative review in the *Journal of Clinical Medicine*, which synthesized the emerging physiologic, anatomical, and mechanistic evidence, demonstrated that optimizing airway function through craniofacial and cervical manipulations may play a valuable role in respiratory care by enhancing airway patency, autonomic regulation, and immune drainage. These actions were especially prominent in asthma and pneumonia.

EVIDENCE AND CONTROVERSIES

CST is a gentle, light-touch technique that complements medical and pharmacological treatment. It is generally considered a low-risk intervention when performed by trained practitioners. It is reported that adverse effects are rare and mild, such as transient dizziness or nausea. Nevertheless, CST is contraindicated in individuals with certain conditions, including intracranial aneurysms, acute brain injury, or bleeding disorders. The concept of CST, pioneered by Southerland and Upledger, also inspired high-quality basic research focused on the functions of the cranial system.

The most recent studies have identified direct connections between the dura mater and the brain (33). The central nervous system barriers listed above in this article were, according to current dogma, thought to prevent nerve cell interactions with the peripheral immune system. Specifically, the arachnoid barrier delineates the border between the central nervous system and dura mater. However, it was demonstrated that tracers injected into the CNS or the CSF drain to cervical lymph nodes, indicating that, despite the presence of the above barriers, the peripheral immune system surveils the brain.

A recent study, published in *Nature*, used novel transgenic mice to examine anatomical structures that facilitate passage across the arachnoid barrier (33). That study demonstrated that the bridging veins create discontinuities, termed arachnoid cuff exit (ACE) points, that cross the arachnoid barrier. The ACE points allow the exchange of fluids and molecules between the subarachnoid space and the dura. Furthermore, in healthy human volunteers, the MRI tracers in the bridging veins crossed similarly to access the subarachnoid space. Importantly, in neuroinflammatory conditions such as experimental autoimmune encephalomyelitis, ACE points also enable immune cells to enter the subarachnoid space directly from the dura mater. This critical study identified direct connections between the dura mater and the brain This study's findings have important mechanistic implications for Alzheimer's disease, aging, neurodegenertive and neuroinflammatory disorders, including multiple sclerosis (33).

Another study demonstrated that, in a migraine model, Trigeminal ganglion neurons are directly activated by the influx of CSF solutes. Furthermore, the studies indicated that meningeal lymphatic CGRP signaling induces pain *via* cerebrospinal fluid efflux and neuroinflammation. Nelson-Money and coworkers demonstrated that in migraine models, calcitonin gene-related peptide (CGRP) signals pain through cerebrospinal fluid efflux and neuroinflammation. These findings indicated an essential role of lymphatics in chronic migraine, whereby CGRP signaling primes MLV-immune interactions and reduces CSF efflux (34).

In the craniosacral system, the glymphatic system serves as a waste-clearance pathway. In the brain, it primarily functions during sleep, removing metabolic waste and maintaining neural function. The name „glymphatic" reflects its dependence on glial cells (mainly astrocytes) and its functional similarity to the peripheral lymphatic system. The glymphatic system, involving aquaporin 4 (AQP4), facilitates the exchange of CSF with interstitial fluid, providing a pathway for the removal of proteins such as amyloid-beta and tau that accumulate in the brains of Alzheimer's disease patients (19 - 21, 36, 37).

The blood-brain barrier (BBB) is formed by a specialized complex of cells and structural components that together create a selective, semipermeable membrane between the brain and the circulatory system (37-39). This complex, known as the

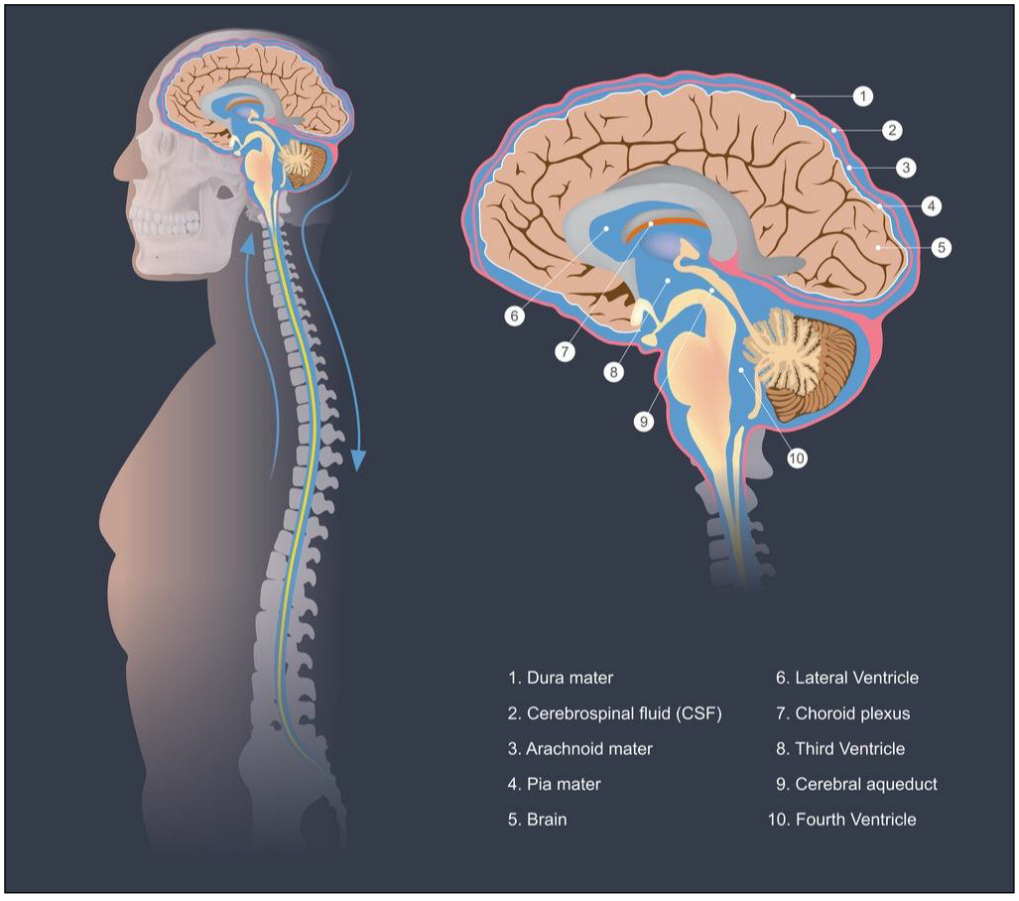

Fig. 1. A diagram of the craniosacral system [iStock.com/BKK1979].

neurovascular unit, consists of endothelial cells lining the brain's capillaries, which are the principal component of the BBB. In contrast to endothelial cells in other parts of the body, brain endothelial cells are unique because they have: tight junctions - specialized connections between the cells that effectively seal the gaps and prevent the unrestricted passage of most substances from the blood into the brain. They also lack fenestrations, which prevent the free diffusion of molecules across the vessel walls, and have low pinocytic activity, thereby reducing the transport of substances *via* vesicles (37-39). Astrocytes, the glial cells, extend projections that almost completely encircle the brain's capillaries. They provide biochemical support to endothelial cells and help induce and maintain tight junctions that create the barrier's unique selective permeability. Pericytes play a similar role to astrocytes and secrete extracellular matrix. Microglia and neurons, components of the neurovascular unit, contribute to the barrier's function. All these components work together to maintain a protective environment for the central nervous system (37-39).

POTENTIAL FUTURE RESEARCH DIRECTIONS IN CRANIOSACRAL THERAPY

Although CST has gained increasing attention as a complementary therapeutic modality, scientific evidence regarding its neurophysiological and biochemical mechanisms remains limited. To establish an evidence-based understanding of CST, further research using advanced neuroimaging, biochemical, and biophysical methods is warranted. The following sections outline key areas for investigation that could clarify the underlying mechanisms and physiological effects of CST. In this article, the authors propose the following studies and techniques to examine the underlying mechanisms and physiological effects of CST.

– Investigation of theta and other brainwave activity during or following CST sessions using quantitative electroencephalography (qEEG).

Preliminary clinical observations have reported that theta brain waves (4–8 Hz) are associated with deep relaxation, creativity, emotional processing, and the transitional state between wakefulness and sleep. These states align closely with CST's therapeutic aims of facilitating emotional and physical release. CST's gentle, light-touch techniques activate the parasympathetic "rest-and-digest" response, corresponding to slower brainwave frequencies such as alpha and theta. Notably, the "still point induction" technique – a temporary pause in the craniosacral rhythm – has been linked to increases in theta amplitude. However, rigorous experimental evidence confirming a causal relationship remains limited. Future studies using quantitative EEG (qEEG) should aim to measure changes in theta, alpha, and other frequency bands during CST, employing control conditions to distinguish CST-specific effects from generalized relaxation responses. Such investigations may help elucidate CST's influence on neurophysiological states related to consciousness, relaxation, and emotional integration.

– Sequential release of β-endorphins and dopamine before and after CST treatment. Endorphins and dopamine play essential roles in pain modulation, stress regulation, and reward mechanisms. β-endorphins (β-E), synthesized in the pituitary gland and hypothalamus, act on opioid receptors to alleviate pain, whereas dopamine contributes to feelings of motivation and pleasure. The interaction between these two neurotransmitters forms a feedback loop linking pain relief to emotional well-being. Based on this literature, evidence suggests that β-E may not only be helpful for acute and persistent pain, but also for a variety of chronic pain states in which opioids are not effective. Investigating the temporal sequence of β-endorphin and dopamine release before and after CST sessions could provide valuable insight into CST's potential biochemical mechanisms. Studies employing blood plasma or cerebrospinal fluid assays could determine whether CST elicits measurable changes in these neurochemicals, thereby supporting its purported analgesic and mood-regulating effects.

– Effects of CST on mitochondrial function in fascia and muscle tissue.

The fascia, including the craniosacral fascial system, is a complex network of connective tissue rich in fibroblasts and mitochondria. Mitochondria play a crucial role in cellular energy production and tissue repair; however, mitochondrial dysfunction

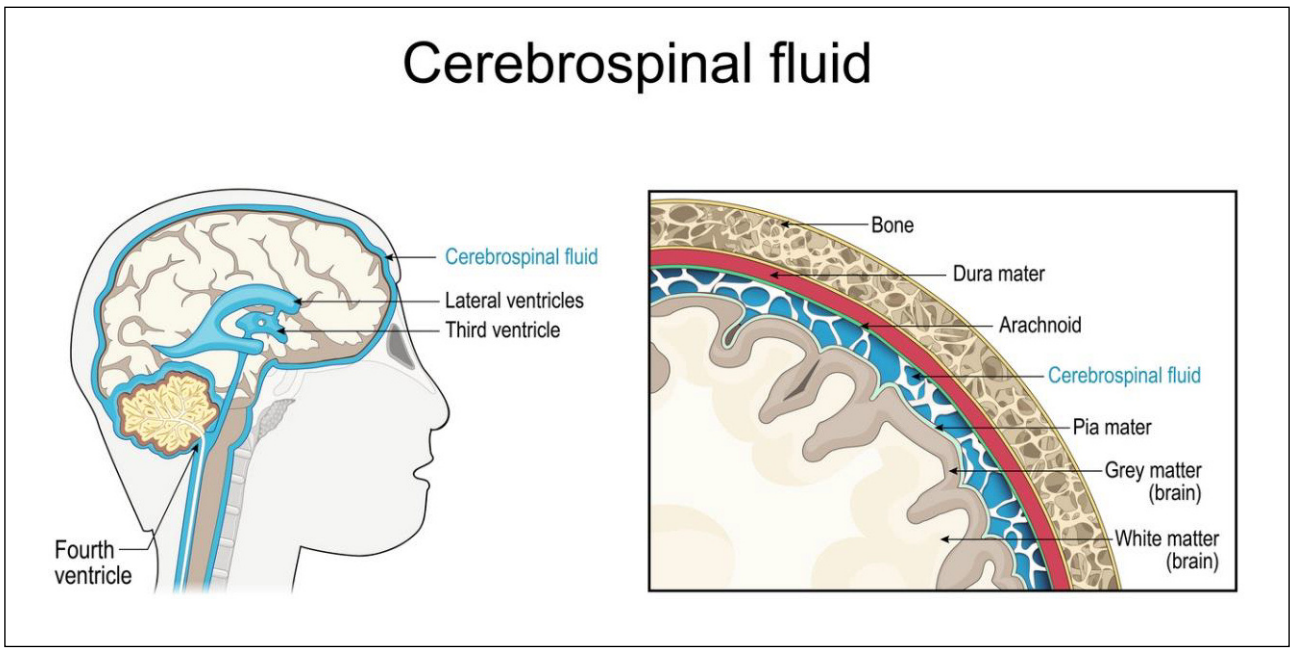

Fig. 2. Craniosacral system and cerebrospinal fluid (iStock.com/ttsz).

is implicated in chronic pain syndromes, such as myofascial trigger points (MTrPs). Mitochondrial damage can lead to reduced adenosine triphosphate (ATP) production, oxidative stress, inflammation, and localized hypoxia. Some publications suggest that manual therapy interventions may reduce pain and pressure pain threshold in patients with myofascial trigger points (40). The effect of CST on mitochondrial status and damage has not been thoroughly examined. Future studies could employ biochemical, histological, or imaging-based methods to determine whether CST enhances mitochondrial function in fascial or muscular tissue, potentially contributing to pain relief and tissue regeneration. Mitochondrial dysfunction has been implicated in chronic pain syndromes, including myofascial trigger points (MTrPs). CST is a complementary treatment approach, and we hypothesize that its therapeutic effects may be enhanced when combined with coenzyme Q10 (CoQ10). We intend to explore this combined intervention in future research. CoQ10 is a naturally occurring molecule essential for mitochondrial energy production and a potent endogenous antioxidant. It plays a crucial role in the generation of adenosine triphosphate (ATP), the body's primary energy source. It helps neutralize free radicals, thereby protecting cells from oxidative stress associated with aging and various pathological conditions.

– *Utilization of high-sensitivity sensors for quantifying fascia and dural movement*.

Practitioners of CST report detecting subtle pulsations in fascial and dural structures through palpation. The development of high-sensitivity sensors capable of objectively measuring these micro-movements would represent a significant advancement in CST research. Such sensors could quantify the amplitude and frequency of fascial oscillations and evaluate the electrical potential of dural membranes (41). This approach would provide empirical data to validate or refine current practitioner-based observations.

– *Measurement of skin electrical potential differences between therapist and patient in the contact area*.

CST involves sustained physical contact, raising the possibility of bioelectrical interactions between therapist and patient. Measuring skin potential differences at points of contact could help determine whether CST induces measurable electrical changes associated with the craniosacral rhythm (42). This line of inquiry may also shed light on potential mechanisms of physiological synchrony during treatment.

– *Simultaneous quantitative encephalography* (*qEEG*) *monitoring of therapist and patient*.

Simultaneous EEG monitoring of both the therapist and the patient during CST sessions could reveal patterns of neural synchronization or co-regulation. Investigating inter-brain coupling and rhythmic entrainment may elucidate the neural correlates of shared therapeutic states. Such studies could enhance understanding of the relational and neurophysiological components underlying the CST process.

– *Application of multimodal neuroimaging techniques* (*EEG-PET-MRI*) to CST.

Recent advances in neuroimaging have enabled the observation of rapid neuronal and metabolic dynamics with unprecedented precision. In a recent paper in *Nature Methods*, the authors used simultaneously functional [^{1}8F] fluorodeoxyglucose (FDG)-based positron emission tomography (PET) - (fPET)-FDG that enables the monitoring of rapid glucose uptake dynamics in humans within a one-minute time frame with unprecedented precision and very high imaging sensitivity (43). They also used EEG-PET-MRI simultaneously to identify temporally coupled and spatially structured brain hemodynamics and glucose uptake. The multimodal imaging and analytical framework established in that study demonstrated how neuronal, hemodynamic, and metabolic dynamics interact to mediate cognition and consciousness, at a temporal resolution previously unfeasible in humans. The application of these methods and techniques to the assessment of CST, during and following CST treatment, would provide entirely novel, fundamental data.

– *Investigation of biochemical markers in CSF*.

CST is proposed to influence the circulation and composition of cerebrospinal fluid. Future studies could examine CSF samples before and after CST interventions to identify biochemical markers associated with changes in CSF flow, composition, or function. Quantifying such markers may clarify CST's potential impact on CSF dynamics and central nervous system homeostasis.

– *Use of confocal laser microscopy in animal models*.

Confocal laser endomicroscopy allows real-time, *in vivo* visualization of cellular and connective tissue structures at

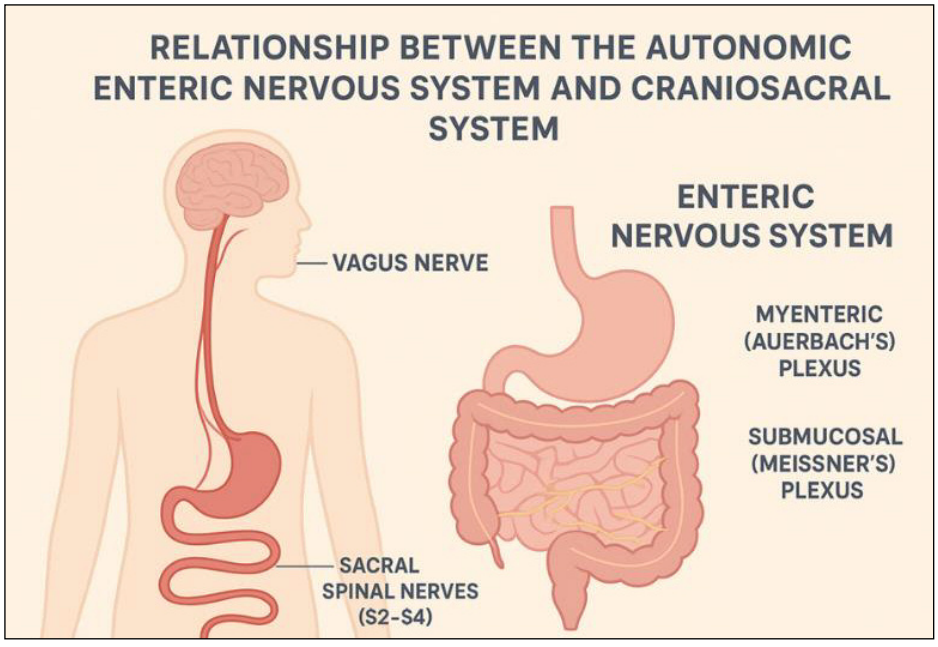

Fig. 3. Autonomic enteric nervous system and craniosacral system. [Credit - Figure generated by ChatGPT].

magnifications up to 1000×. Applying this technique to animal models receiving CST could enable direct observation of fascial, vascular, and neuronal responses at the cellular level. This approach would provide valuable mechanistic insights into how CST influences tissue physiology. Some studies show it is technically feasible to image the enteric nervous system, including nerve networks, ganglia, and glial cells in living tissue using endoscopic CLE (44, 45).

– *Investigating the role of prostanoids and specifically prostacyclin in the cranial system and potentially in CST.*

Prostanoids are a group of biologically active lipid compounds synthesized from arachidonic acid, a 20-carbon polyunsaturated fatty acid. They play key roles in inflammation, vascular tone, platelet function, smooth muscle activity, and other physiological processes. While the craniosacral system and prostanoids belong to different physiological fields (neuroanatomical vs. biochemical/vascular), they can interact indirectly through shared vascular and inflammatory pathways (46-51). Prostacyclin - prostaglandin I_2 (PGI_2) is a prostanoid (a type of eicosanoid) derived from arachidonic acid through the cyclooxygenase pathway in endothelial cells lining blood vessels. It induces vasodilation by relaxing vascular smooth muscle, thereby lowering blood pressure and improving blood flow. It also inhibits platelet aggregation, preventing blood clotting within vessels. Furthermore, it exerts a cytoprotective effect, protecting vascular endothelium and other tissues from damage. In addition, it opposes thromboxane A_2 (TXA_2), which promotes vasoconstriction and platelet aggregation. Thus, the prostacyclin vasodilatory action on cerebral vessels can influence intracranial pressure and CSF dynamics and may indirectly affect CSF production and circulation within the craniosacral system. Furthermore, prostacyclin has anti-inflammatory and neuroprotective properties, which may reduce inflammation in meningeal vessels and support the integrity of the blood-brain barrier. Since prostacyclin release is modulated by autonomic signals, stress or parasympathetic activation could influence both systems. The craniosacral system interfaces with the autonomic nervous system. Because prostacyclin is a vasodilator and anti-inflammatory mediator acting on the cerebral vasculature, it can modulate several processes that directly affect the craniosacral system – namely cerebral blood flow, meningeal perfusion, CSF dynamics, and neuroinflammation. Although prostacyclin does not directly control CSF secretion, it modulates choroid plexus blood flow. Enhanced perfusion can increase CSF turnover and waste clearance through the glymphatic system. In conditions such as idiopathic intracranial hypertension, prostacyclin analogs may theoretically help optimize venous drainage, thereby indirectly reducing CSF pressure. While craniosacral therapy (CST) focuses on manual techniques to balance CSF flow and meningeal tension, prostacyclin physiology represents a biochemical route to similar goals – optimizing vascular tone, reducing inflammation, and supporting rhythmic fluid dynamics (46-51). Thus, from an integrative physiology perspective, Prostacyclin supports the fluid and vascular balance that the craniosacral system depends on, as shown in the conceptual diagram below: prostacyclin → vasodilation → improved cerebral perfusion → stable ICP → balanced CSF flow → reduced meningeal tension → craniosacral homeostasis.

Despite these theoretical considerations, the precise role of prostacyclin in the craniosacral system and craniosacral therapy remains unexamined.

The proposed research directions integrate neurophysiological, biochemical, and biophysical perspectives to establish a more rigorous scientific foundation for craniosacral therapy. By employing advanced analytical tools – such as qEEG, PET-MRI, biochemical assays, and micro-sensor technology – future studies could validate or refine CST's theoretical framework. Such evidence would significantly contribute to understanding the biological mechanisms underlying CST and its reported therapeutic outcomes.

In this article, we also aimed to clarify the relationship between the craniosacral components of the autonomic nervous system (ANS) and the enteric nervous system (ENS), and to provide a brief overview of emerging techniques for visualizing ENS structure and function. The CNS – comprising the brain and spinal cord – integrates sensory inputs and coordinates physiological responses. The autonomic nervous system (ANS), a major division of the peripheral nervous system, regulates involuntary processes such as cardiovascular function, respiration, secretion, and gastrointestinal activity. It consists of sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions (52 - 56).

The enteric nervous system is traditionally classified as a division of the ANS; however, its capacity for autonomous reflex activity has led some authors to consider it a semi-independent branch of the nervous system (52 - 56). The ENS contains approximately 500 million neurons and is organized into two major plexuses: (i) the myenteric (Auerbach's) plexus, which primarily regulates gastrointestinal motility, and (ii) the submucosal (Meissner's) plexus, which regulates secretion, ion transport, and local blood flow. Although capable of intrinsic activity, the ENS is continuously modulated by extrinsic autonomic inputs. Sympathetic fibers generally inhibit gastrointestinal motility and secretion, whereas parasympathetic fibers exert predominantly excitatory effects that facilitate digestion (55, 56).

The parasympathetic division is termed "craniosacral" due to its anatomical origin. The cranial component is dominated by the vagus nerve (cranial nerve X), which conveys approximately 75% of all parasympathetic outflow and provides the principal bidirectional communication pathway between the brain and the gastrointestinal tract. Vagal afferents relay sensory information from the gut to the CNS, whereas vagal efferents modulate enteric circuits, influencing motility, secretion, and inflammatory responses. The sacral component, arising from the pelvic splanchnic nerves (S2–S4), innervates the distal colon, rectum, and pelvic organs, coordinating colonic motility, defecation reflexes, and visceral sensation.

Together, the ENS and the craniosacral parasympathetic pathways constitute a major component of the gut-brain axis, a bidirectional network linking neural, endocrine, immune, and metabolic signaling between the gastrointestinal tract and the CNS. This integrated system ensures that digestive processes are dynamically matched to the organism's physiological state, stress responses, and metabolic needs (52 - 56).

NOVEL METHODS AND TECHNIQUES FOR VISUALIZING THE ENTERIC NERVOUS SYSTEM

Advances in optical, molecular, and computational methods have greatly improved the ability to characterize ENS structure and function. Key approaches include:

1. Tissue-clearing methods (*e.g.*, CLARITY, iDISCO, CUBIC). These techniques render intestinal tissue optically transparent, enabling three-dimensional visualization of neuronal networks in intact gut segments when combined with confocal or light-sheet fluorescence microscopy.

2. Light-sheet fluorescence microscopy (LSFM). SFM permits rapid, high-resolution imaging of large tissue volumes with reduced phototoxicity. It is increasingly used to reconstruct ENS architecture and assess region-specific neuronal density and organization.

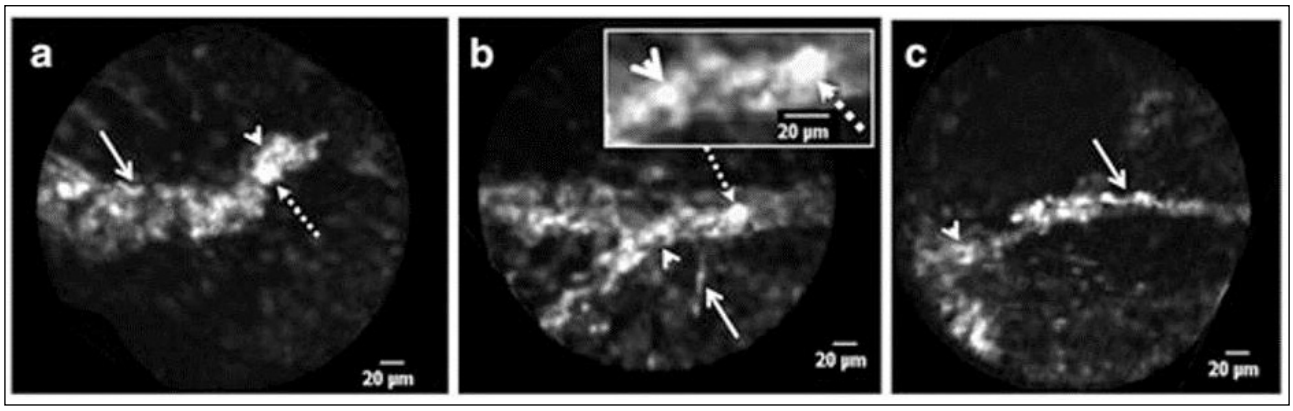

Fig. 4. Needle-based confocal laser endomicroscopy images of the gastric enteric nervous system (GENS) – submucosal Meissner's plexus. (a): Representative image demonstrating visualization of the GENS. The gastric neural network comprises neuronal cells, glial cells, and nerve fibers. (b, c): Representative images showing thick, branching GENS structures. Arrowheads indicate neuronal cell bodies; arrows indicate nerve fibers; and dotted arrows indicate glial cells. The inset in panel (b) shows a neuronal cell (arrow) and a glial cell (dotted arrow) at higher magnification. Neuronal cells exhibit intense NeuroTrace staining in the cytoplasm but not in the nuclei, whereas glial cells (both cytoplasm and nuclei) stain strongly with NeuroTrace. [Reproduced from J. Samarasena *et al.*, *J Gastroenterol Hepatol*, ref. 45].

3. Two-photon microscopy. Two-photon imaging enables deep-tissue visualization and is suitable for live or semi-intact preparations, facilitating the real-time observation of enteric neuronal and glial activity.

4. Genetically encoded calcium indicators (GECIs). Indicators such as GCaMP enable dynamic imaging of neuronal and glial signaling in the ENS, revealing activity patterns underlying motility, reflexes, and gut-brain communication.

5. Spatial transcriptomics and multiplexed RNA imaging. Technologies such as MERFISH, Slide-seq, and Visium support high-resolution mapping of ENS cell types and reveal molecular heterogeneity across intestinal regions.

6. High-resolution immunofluorescence with computational reconstruction.

7. Needle-based confocal laser endomicroscopic imaging *in vivo* of ENS after injection of NeuroTrace (45) (*Fig. 4*).

Advances in antibody panels, volumetric imaging, and analysis pipelines allow quantitative assessment of ENS cell populations, neurotransmitter expression, and microcircuit organization. These technologies provide extraordinary insight into ENS structure and function.

In our previous study, we used a needle-based confocal laser endomicroscopy (nCLE) probe to visualize neuronal cells and nerve fibers in the gastric enteric nervous system for the first time *in vivo* (45).

The recent communications and updates from the Upledger and the Upledger-Barral Institutes have drawn attention to a study in which investigators directly measured rhythmic motions of the human head and reported evidence of a distinct third physiological rhythm, corresponding to the craniosacral rhythm (57). More recently, Dr. Thomas Rasmussen, Director of Research at the Upledger Institute International, proposed the Pacemaker Theory of the craniosacral rhythm. This theory proposes that the CSR is generated by specialized populations of oscillatory neurons in the brainstem, near the fourth ventricle. These neurons are hypothesized to function as an intrinsic pacemaker system operating independently of respiratory and cardiac rhythms. According to this theory, such neuronal populations act as endogenous biological oscillators, producing stable rhythmic activity that may contribute to the regulation of fundamental physiological processes. The CSR is proposed to propagate throughout the body *via* vascular pathways and to play a critical role in supporting systemic balance and physiological vitality. In this context, CST is an intervention designed to engage with this rhythm, aiming to facilitate the body's inherent capacity for self-regulation and homeostasis.

The craniosacral system plays a crucial role in protecting and maintaining the function of the central nervous system. While the anatomical and physiological basis of the craniosacral system and CSF circulation is well established, the theoretical framework underlying CST remains partially speculative. Although clinical reports indicate potential therapeutic benefits, the lack of robust, high-quality evidence underscores the need for further interdisciplinary research employing advanced imaging, physiological measurement, that we proposed, and randomized controlled trials to clarify the mechanisms and efficacy of CST.

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