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Autonomic nervous system and viscera-related responses to manual therapy: A narrative overview

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ABSTRACT

Background: Manual therapy (MT) has long-held that it physiologically impacts autonomic nervous system (ANS) and viscera-related function. This narrative review is intended to serve as a consolidated interdisciplinary resource of original studies related to physiological effects of MT as it relates to the ANS for MT clinicians and researchers new to this MT-related topic.
Objective: This review seeks to identify ANS and viscera-related physiological responses to MT interventions using search terms commonly used by chiropractic, massage, osteopathic, physical therapy, and structural integration clinicians and to provide a quick reference resource of original MT-related studies investigating ANS effects.
Methods: For this interdisciplinary review, the search was limited to the largest and most commonly used database (PubMed) between years 2000 and 2024, with a focus on direct ANS-related physiological outcomes. Unlike systematic reviews, assessment of scientific rigor and potential bias of included articles was beyond the scope and purpose of the current work.
Results: Original MT-related studies provide mixed evidence with regards to immediate and/or short term ANS and/or viscera-related responses on blood pressure, heart rate variability, skin conductance/temperature, respiratory and lymphatic changes.
Conclusions: This review identified a large number of MT and ANS-related original research in PubMed. Careful study of original MT-related research is needed with particular attention focused on the standardization of MT methodological approaches, appropriate controls, study design, appropriate populations, MT techniques, and anatomical site delivery so as to design more rigorous studies in order to arrive at definitive conclusions regarding direct effects of MT on the ANS.

Implications for practice

- To provide an interprofessional reference resource of original research for manual therapy clinicians and researchers new to the field interested in autonomic and visceral responses to manual therapy.
- Increase manual therapy practitioner awareness, knowledge, and understanding of the current evidence of manual therapy effects on the autonomic nervous system.

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- Allow manual therapy clinicians and researchers to evaluate and correct past limitations of original MT research so as to design more rigorous studies in specific populations.

1. Introduction

Somatosensory reflexes associated with manual therapy (MT) treatment in its various forms (spinal manipulation, joint mobilization, massage, etc.) have long been theorized by MT practitioners such as chiropractic, massage, osteopathic medicine, physical therapy, and structural integration to alter the function of the autonomic nervous system (ANS) [1–4]. The ANS is traditionally divided up into the sympathetic, parasympathetic, and enteric nervous systems which are responsible for maintaining a homeostatic internal environment of the body. The anatomical and functional complexity of the ANS and its relationship with force-based MT presents many interdisciplinary research challenges, especially when coupled with a lack of universally accepted MT intervention-related terminology, lack of methodological standardization of MT treatment (within and across MT-related professions), and the differences in ANS responses elicited during MT treatment of asymptomatic and symptomatic individuals. These challenges and complexities are well noted in a number of MT and ANS systematic literature reviews [5–10], as well as in a recent overview of systematic reviews of MT effects on ANS function [11].

Common ANS measures used in MT-related studies include heart rate variability (HRV), respiratory rate (RR), heart rate (HR), systolic/diastolic blood pressures (BP), oxygen saturation (SpO2), pupillary reflexes, skin conductance and blood flow as primary indicators of sympathetic and parasympathetic function. For a more complete list of ANS markers and their interpretation see Roura et al. [11]. While there is strong agreement regarding markers of ANS activity, differences in measures and methodologies, data interpretation, MT-related interventions and ideal populations to be investigated have contributed to the present state of ambiguity and lack of definitive conclusions regarding the effects of MT on the ANS. This indicates a need for more original interdisciplinary research on the topic of MT and ANS function.

Therefore, in an attempt to encourage greater interdisciplinary collaboration and begin to dismantle long-standing inter-professional barriers between the different manual therapy professions, the A.T. Still Research Institute, Kirksville, Missouri initiated an effort in 2018 to create an International Consortium of Manual Therapies (ICMT) comprised of academic, clinical, and research members from the United States and Europe. The ICMT mission is one of striving to promote scientific dialogue, clarification, knowledge, and consensus among the various manual therapy professions [12]. Despite countless MT approaches, it is thought that many manual therapies share similar physiological mechanisms due to a high degree of overlap in MT application techniques. However, much more mechanism-related research is needed to either confirm or reject such speculation. Current mechanism-related thought suggests that MT impacts ANS function through physiological mechanisms such as improving hypothalamus-pituitary-adrenocortical axis function [13], decreasing sympathetic tone/hypertoncity (which may improve endothelial function), somatosensory reflexes, and/or vagal functioning via increasing parasympathetic function and/or ameliorating dysregulated autonomic activity [1,2,14–16]. Generally speaking, most MT studies suggest a decrease in sympathetic influence and enhanced parasympathetic modulation promoting relaxation that accompanies reduced sympathetic nerve activity [17–19]. One must remain mindful that any type of MT treatment that induces relaxation regardless of approach will impact ANS regulation and that psychological expectation and experience resulting in a physiological effect can challenge claims that a specific MT intervention is causal in specific outcomes [20], but reviewing this aspect is beyond the scope of the current review. With that said, this narrative review is intended to serve as a consolidated resource of original interdisciplinary studies related to direct physiological effects of MT as it relates to the ANS and/or viscera function specifically for MT practitioners and non-manual therapy researchers interested in this area of research.

2. Materials and methods

The primary purpose of this narrative review is to identify original research articles in the PubMed literature regarding MT and direct physiological ANS-related changes. A unique feature of the review search strategy was that it was specifically devised to allow for cross matching manual therapy profession-specific (chiropractic, massage therapy, osteopathic, physical therapy, and structural integration) terminology with ANS-related categories as identified by the ICMT researchers. The specific search hedges for each MT profession and category are provided in a Supplementary File. For this particular narrative review, the search was limited to the PubMed database so as to focus our ICMT team efforts on the largest and most commonly used database across all MT-related professions. The ultimate purpose of this review was not to perform an exhaustive search of all available complementary and integrative health literature, which would entail additional searches involving multiple databases from inception and article retrieval from profession-specific journals. For this initial ICMT review, focus was also placed on direct physiological measures of autonomic nervous system (ANS) related changes associated with MT, to the exclusion of patient-centered outcomes which will be addressed in future studies. The initial searches were performed in January 2021 by two team members (LL, MA) with updated searches performed in July of 2024. Search results were provided to ICMT team members (MA, BD, EJ, SF, NK, VK, WR) in an excel spreadsheet format with the combined search hedges linked to the results. Team members transferred articles meeting the inclusion criteria into PaperPile Reference Manager software categorized subfolders organized by two team members (GF, BD). Abstracts were screened for articles meeting the following inclusion criteria: (a) human studies (excluding pediatrics due to developmental changes occurring), b) peer-reviewed research; (b) published in English; (c) inclusion of ANS or viscera-related physiological measures; (d) indexed in the PubMed database; (e) published between 2000 and 2024; (f) directly relate to human physiology changes. Case studies and studies that involved only combined treatments of manual therapy and/or other interventions/modalities were excluded. Fig. 1 shows a flowchart of the review process. Team members worked collectively in incorporating, organizing, and reviewing research findings from articles meeting inclusion criteria into a draft narrative review manuscript that was subsequently refined and edited.

3. Results

3.1. Cardiovascular system

3.1.1. Blood pressure

In humans, many MT studies report increases or decreases in systolic and/or diastolic BP in normotensive adults and those with/without acute pain [18,21–27], or with hypertensive individuals [28–32] (Table 1). A review of literature from 1980 to 2019 identified 27 non-case studies investigating the effects of high velocity low amplitude thrust spinal manipulation (HVLA-SM) on hypertension with the number of study participants ranging from 11 to 331 [33]. Significant changes in BP were reported in 14/27 of studies [33]. A separate systematic review and meta-analysis in the same year indicated a statistically significant decrease in systolic BP, but not with diastolic BP or heart rate following HVLA-SM and/or spinal mobilization [34]. Multiple studies reported no significant BP changes following HVLA-SM, osteopathic manipulative therapy (OMT), joint mobilization, and/or other forms of MT in normotensive individuals with/without musculoskeletal pain [35–44], pre-hypertensive/stage 1 hypertensive individuals [45,

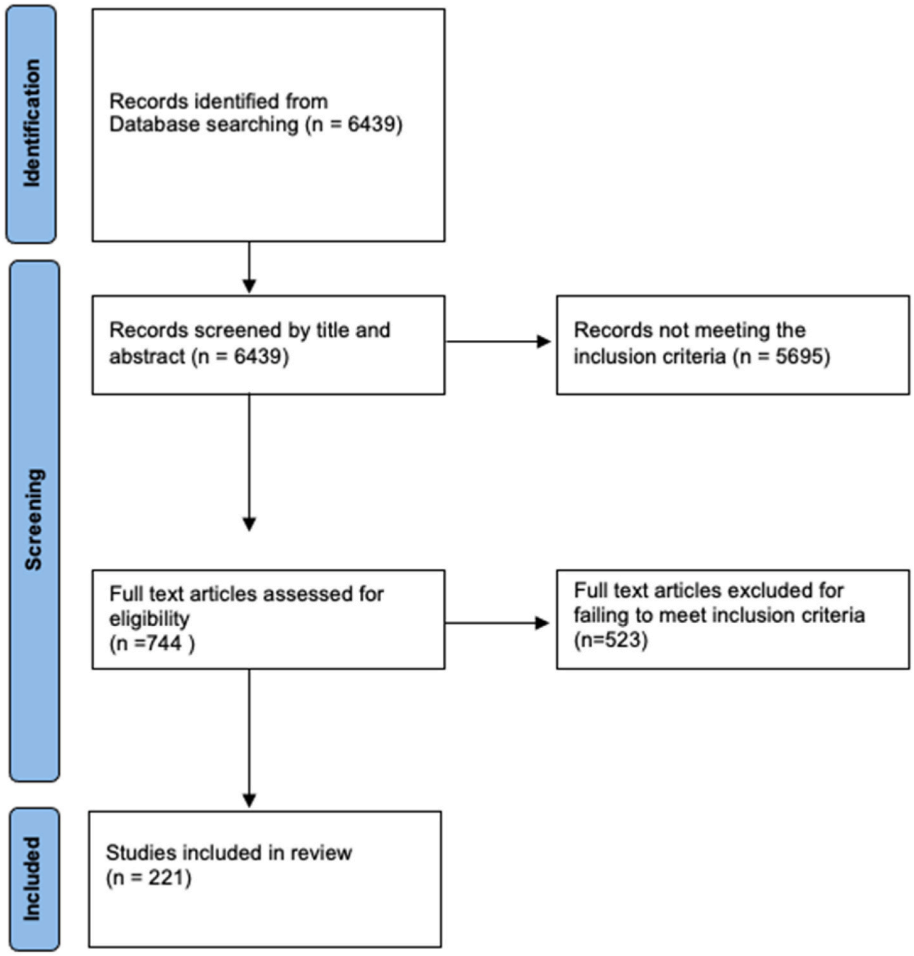

Fig. 1. Flowchart diagram.

Table 1
Evidence suggesting SBP and DBP changes following Manual Therapies.

Type of Manual Therapy	SBP and/or DBP Increase	SBP and/or DBP Decrease	No Change in SBP or DBP
HVLA-SM		[21,22,24,25, 28–30]	[35,37,39,40, 45–48]
Joint Mobilization		[18,23]	[36]
OMT		[26,27,31,32]	[38,41–44]
Massage		[50–87]	[88–104]

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HVLA-SM: High Velocity Low Amplitude Thrust Spinal Manipulation; OMT: Osteopathic Manipulative Therapy.

46], or hypertensive individuals [47,48] (Table 1). A recent study in third trimester pregnant women found that OMT (30–40 min) significantly decreased diastolic BP and HR and increased systolic BP in the sitting position, while decreasing it in the supine position (all changes remaining within normal parameters) [49]. In addition to these aforementioned studies, no differences in cardiovascular parameters (including BP) were reported comparing anterior-posterior versus lateral cervical non-thrust mobilization techniques [18].

In another systematic review of 24 English and Chinese articles published before December 2013 involving massage therapy for essential hypertension, massage alone and/or in combination with antihypertensive drugs appeared to be more effective than no intervention or antihypertensive drugs alone in lowering systolic BP [105]. However, poor methodological quality was noted in a majority of these studies, thereby limiting definitive conclusions due to lack of scientific rigor [105]. Subsequent systematic reviews of massage therapy effects on essential hypertension describe similar inconsistencies among reported outcomes as well as methodological quality issues thereby limiting any conclusions [106,107]. A 2019 review of 13 systematic reviews of 14 non-drug therapies (including massage) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria [108], found sufficient evidence that either massage or acupuncture with an antihypertensive drug could benefit individuals wanting to lower their BP [109]. Similar to the aforementioned other forms of MT, a number of massage studies reported significant decreases in systolic and/or diastolic BP [50–87], or no changes in systolic and/or diastolic BP following massage [88–104] (Table 1). However, it should be noted that many of these studies failed to include a control group. Duration of BP effects related to massage appear to be transitory, lasting minutes to hours, however at least one study has reported massage BP effects lasting days [51].

Similar to BP studies, HVLA-SM, joint mobilization, OMT, and massage changes on HR were mixed with some reporting an increase, a decrease, or no change in HR following the intervention (Table 2).

3.1.2. *Heart rate variability*

Heart rate variability (HRV) is the variation of time between consecutive heartbeats and it serves as a common marker of ANS function [126,127]. Short-term changes in HRV low frequency (LF) and high frequency (HF) components in relation to HVLA-SM, joint mobilization, OMT, and massage have been reported (Table 3). Increases in the LF/HF ratio was demonstrated after various types of MT in healthy adults [4, 128,129], while the LF/HF ratio decreased after MT in asymptomatic

Table 2
Evidence suggesting HR changes following Manual Therapies.

Type of Manual Therapy	HR Increase	HR Decrease	No Change in HR
HVLA-SM	[110, 111]		[17,21,29,35,39, 40,47,112]
Joint Mobilization	[113, 114]	[36,115]	[23]
OMT		[26,42,116–118]	[38,43,44,119, 120]
Massage	[86,121, 122]	[58–61,63,67,68,70–76, 78–80,82,85,87–89,96,104, 121,123]	[56,65,83,92–95, 97–103,124,125]

HR: Heart Rate; HVLA-SM: High Velocity Low Amplitude Thrust Spinal Manipulation; OMT: Osteopathic Manipulative Therapy.

Table 3
Evidence suggesting HRV changes following Manual Therapies.

Type of Manual Therapy	LF/HF ratio Increase	LF/HF ratio Decrease	No Change in HRV
HVLA-SM	[4,128]	[21,24,40,114, 133,134]	[13,39,112, 135–140]
Joint Mobilization		[115]	[141]
OMT	[129]	[14,117, 130–132]	[32,41,42,116, 119,120]
Massage	[60,85,124,125, 142–149]	[60,65,84,123, 144,148]	[91,150–152]

HR: Heart Rate Variability; HVLA-SM: High Velocity Low Amplitude Thrust Spinal Manipulation; OMT: Osteopathic Manipulative Therapy.

and symptomatic participants [14,21,24,40,114,115,117,130–134].

However, no significant HRV changes were reported in other studies yielding mixed results overall (Table 3). A single OMT treatment in individuals with heart failure demonstrated immediate increases in flow-mediated dilation at the brachial artery and greater peak diameter thereby effectively increasing brachial blood flow along with some relevant HRV modulation occurring 15 min after OMT delivery [153]. These findings suggest that OMT-induced vascular changes may precede autonomic modulation. However, in another randomized clinical trial using a single OMT treatment focused on using myofascial release technique on individuals with heart failure, there were no inter- or intra-group differences in the resistive index of the brachial, carotid, and femoral arteries, as well as no differences in BP and HR measures [154]. In a study investigating the immediate effect of T2, T5, T11 thoracic spinal manipulation vs. sham treatment on healthy individuals, there was a significant increase in root mean square of successive difference (RMSSD) in the manipulation group [155]. Another study in healthy adults using RMSSD (which assesses vagal activity with increases indicating parasympathetic activation) as a measure of HRV following a OMT technique (suboccipital balanced ligamentous tension) or a measured breathing technique, there were no significant differences between or within groups [156]. Similarly a separate OMT study (using osteopathic cranial vault hold stimulation) failed to result in any significant RMSSD effect despite significant effects on skin perfusion and respiration outcomes [157].

In a separate massage study, 20 min of postoperative foot massage following a cesarean delivery was reported to lower the LF/HF ratio compared to a control group [84]. In an unrelated study compared to baseline, 15 min of massage for three consecutive nights failed to decrease the prevalence and incidence of dysrhythmia as measured by electrocardiogram, unlike dry cupping sessions using the same treatment parameters [158].

3.2. Integumentary system

3.2.1. Skin conductance/temperature

MT studies resulted in mixed changes in skin conductance (an indicator of sweat gland activity) and changes in skin temperature, with the overall evidence pointing to an effect of MT on the sympathetic nervous system (SNS) [8,9,38,40,113,122,159–176]. In a study investigating the influence of two OMT techniques (fourth ventricle compression (CV4) and rib raising (RR)) compared to placebo on skin conductance in healthy individuals, skin conductance was increased in individuals treated using the CV4 technique [129]. The impact of mobilization rate was also supported by a separate study in which lumbar mobilization at the rate of 3Hz produced significant and greater skin conductance magnitude compared to an application rate of 2Hz [174]. In another study, cervical mobilization at an application rate of 0.5Hz demonstrated increased sympathetic activity (skin conductance, heart rate, breathing rate) compared to sham treatment and was also accompanied by short-term hypoalgesic effects [113]. It should be noted that the multisystem sympathoexcitation response to MT is not restricted to spinal treatment as similar SNS alterations were also reported following elbow mobilization with movement [177]. However, the overall magnitude of SNS-related changes reported with elbow joint mobilization were quite small, so caution must be taken when interpreting these physiological changes in relation to clinical relevance [177]. Anticipated vasoconstriction from sympatho-excitatory mechanisms related to MT was found not to be the case, rather a sympatho-inhibition was reported after spinal mobilization [167]. As a result, using blood flow as an indicator of a strictly SNS response after MT has become questioned as both sympathetic and non-sympathetic mechanisms contribute to regulation of skin blood flow [159].

A small study (n = 11) investigating the effects of HVLA-SM on paraspinal cutaneous temperature in participants with low back pain reported a nonsignificant increase after nine treatments with lower temperatures in individuals with low back pain compared to asymptomatic controls [178]. In a more recent study involving myofascial techniques (Graston Technique and self-myofascial release), skin temperature increased immediately following the both interventions [179]. Connective tissue massage significantly increased skin temperature compared to baseline for up to 60 min in yet another small study (n = 8) [180]. In a somewhat larger study (n = 25), the average temperature of the fascial manipulation treated area increased significantly within 5 min of treatment onset and peaked 24 h after soft tissue manipulation ended, with temperature changes most likely attributed to resultant localized tissue inflammation [179].

3.3. Lymphatic system

The osteopathic profession has developed a series of lymphatic pump techniques (LPT) to enhance lymph flow throughout the body [181]. Immune system effects of LPT in animal models, as well as, humans are reviewed by Hodge [182]. In a pilot OMT study (n = 20) consisting of myofascial release, splenic pump, and pedal lymphatic pump treatment, platelet counts significantly decreased compared to light touch control, while non-significant decreases occurred with absolute lymphocyte cell count, red blood count, hemoglobin and hematocrit measures [183]. Similar decreases in platelet counts, along with increased diastolic blood pressure were reported for 60 min post-OMT treatment [184].

Manual lymphatic drainage (MLD) treatment is centered around elastic deformation of cutaneous and subcutaneous tissues to move lymph fluid and transport it to lymph nodes. MLD intervention resulted in increased diastolic BP when applied to the abdomen, decreased systolic BP and diastolic BP when applied to the neck or leg, a reduction of systolic BP when applied to the arm, and no change in SpO2 levels regardless of where treatment was applied [185]. This implies regional acute cardiovascular effects of MLD treatment. Lower extremity MLD decreased heart rate and limb circumference in patients with heart failure and lower limb edema, while not impacting other hemodynamic parameters [186]. MLD to the neck and abdomen significantly decreased the LF/HF ratio and heart rate variability compared to control [187]. In addition, other cardiac measures such as the cardiac interbeat (R-R) interval, standard deviation of normal-to-normal (SDNN), RMSSD, and pNN50 (%) values were significantly higher in the MLD group compared to control [187]. MLD with upper limb elevation increased brachial vein velocity flow for 30 min in women with breast cancer having had post-auxillary lymphadenectomy lymphedema [188]. MLD applied to the medial and lateral aspects of the thigh increased femoral vein flow volume from baseline, while the femoral vein and great saphenous vein flow was augmented with medial thigh MLD and similar increases experienced when MLD was applied to the medial or lateral aspect of the leg; indicating that MLD increases deep and superficial venous flow [189]. MDL increased cephalic vein velocity compared to control and lowered blood lactic acid and creatine kinase as well as increased muscle strength immediately after exercise [190]. Both MLD and petrissage massage were reported to reduce passive muscle stiffness following exercise in women [191]. MLD was also shown to reduce asymmetric dimethylarginine (ADMA) levels (an indicator of endothelial function/inflammation) over three weeks of treatment [192]. However, no beneficial effects of MLD on inflammation and/or indirect markers of muscle damage after exercise were reported when compared to rest in healthy students playing sports [193]. A study of 60 participants undergoing MLD for 10 and 30 min (3x/week) indicated that 10 sessions of MLD resulted in significantly decreased insulin, 2h-post-load glucose, leptin and HOMA-IR (homeostatic model assessment-insulin resistance) values, suggesting that MLD may have a biochemical effect in normal and overweight individuals [194]. Craniocervical MLD reduced intracranial pressure in patients with severe cerebral diseases while not significantly impacting mean arterial pressure, HR, cerebral perfusion pressure or oxygen saturation [195]. While there appears to be increasing evidence regarding therapeutic benefits of MLD, continued investigations into the physiological mechanisms of MLD are needed.

3.4. Respiratory system

Thoracic HVLA-SM resulted in a significant increase in respiratory rate [110], whereas cervical HVLA-SM failed to alter respiratory rate [130]. Unlike thoracic HVLA-SM and cervical mobilization treatment, massage resulted in significant decreases in respiratory rate [63,67,71,73,75,76,79,82,84,96], or in no changes in respiratory rate [72,74,83,93–95,100,102,104]. In addition, a separate OMT study of suboccipital decompression resulted in no respiratory rate differences following treatment [130].

In healthy subjects, thoracic HVLA-SM resulted in a significant increase in pulmonary function in terms of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) compared to control group [196]. These initial improvements in pulmonary function were supported by a subsequent thoracic HVLA-SM study [197]. In a case series of six patients receiving a course of 12 HVLA-SM treatments over four weeks, there was a short-term improvement of FEV1 in four out of six participants but sustained improvement at four weeks only occurred in one participant [198]. In a separate healthy subjects study, various osteopathic manual techniques (including thoracic HVLA-SM) failed to change FVC and FEV1, but significantly increased peak expiratory flow (PEF) compared to the placebo group [199]. HVLA-SM alone or in combination with exercise in healthy individuals increased FVC and FEV1; whereas the exercise alone demonstrated a decrease in FVC [200]. In physically inactive but otherwise healthy individuals, three sessions of thoracic spinal manipulation resulted in no change in FVC and maximum voluntary ventilation (MVV) compared to sham treatment [201]. Increases in FVC were also found in a group of moderate chronic obstructive pulmonary disease (COPD) patients receiving HVLA-SM + soft tissue therapy + exercise compared to soft tissue treatment only and SM + soft tissue [202]. Based on this particular study, MT intervention alone without combining it with exercise appears to have only a small therapeutic benefit in moderate COPD patients [202].

In individuals with neck pain, between group analysis showed that combined thoracic spine mobilization and stretching exercises significantly increased FVC, FEV1, and PEF compared to these treatments being delivered individually [203]. Individuals with hyperkyphosis, thoracic mobilization with movement combined with postural exercise resulted in significant increases in FVC, FEV1, FEV1/FVC ratio, and MVV compared to the sham group receiving postural exercise [204]. These combined intervention studies make it difficult to determine the contribution of individual modalities, but offer a more realistic and potentially more beneficial MT treatment strategy. In post-stroke patients, cervical and thoracic mobilization resulted in a significant improvement in pulmonary function in terms of FVC, FEV1, and peak cough flow as compared to a control group [205]. In this same post-stroke population, a more recent study found that trunk rehabilitation and cervical spine mobilization failed to alter FVC, FEV1, PEF, and maximum expiratory pressure (MEP) [206]. These findings suggest that specific thoracic MT treatment may be required to achieve positive respiratory functional changes, whereas the contribution from cervical treatment is questioned. However that said, in a separate single group study these investigators found that diaphragmatic breathing with cervical mobilization significantly increased FEV1, FVC, and PEF [207], while post-stroke MT study, rib cage joint mobilization resulted in no change in respiratory muscle tone and stiffness [208].

In healthy individuals, OMT and OMT + standard pulmonary rehabilitation improved FVC, and FEV1 more than just standard pulmonary rehabilitation alone [209]. In individuals with pulmonary arterial hypertension, OMT resulted in significant improvements in FVC, FEV1, PEF, HR, SpO2 levels, and fractional exhaled nitric oxide (FeNO) compared to control [210]. Combination of pulmonary rehabilitation + OMT led to a significant decrease in residual volume (RV) of approximately 11 % compared to pulmonary rehabilitation alone, while increases in FEV1 failed to reach significance [211]. Conventional pharmacological treatment combined with OMT demonstrated mixed improvements in physiological outcomes [212]. In cystic fibrosis patients, improvements in spirometry measures were reported in both OMT and sham therapy groups, with no statistically significant differences between groups [213]. A standardized cardiorespiratory rehabilitation program combined with OMT in post-sternotomy patients increased the mean inspiratory volume compared to the cardiorespiratory rehabilitation alone [214]. OMT decreased chronic thoracic pain but failed to improve pulmonary functional outcomes at 12 weeks post-coronary artery bypass graft surgery compared to the standard care group [215]. In a gastroesophageal reflux study, increases in lower esophageal sphincter pressure and average respiratory pressure occurred following OMT on the diaphragm muscle, whereas maximum expiratory pressure did not change [216].

The role of MT in COPD patients has been recently reviewed with transient effects on respiratory rate and heart rate identified with isolated treatments. Mixed results are reported when MT is used in combination with exercise and/or other interventions [217]. In a single group study of patients with severe COPD, a single MT session using joint mobilization and myofascial release technique resulted in a significant improvement in FVC, FEV1, FVC, vital capacity (VC), MEP, maximum inspiratory pressure (MIP) and decreased HR and RR compared to baseline [218]. In a subsequent single group study, subjects with COPD receiving thoracic HVLA-SM combined with muscle energy technique experienced significant improvements in FVC, FEV1, MIP, and SpO2 compared to baseline [219]. Elderly COPD patients treated with seven standardized OMT techniques in a single session experienced significant increases in RV, total lung capacity, and decreases in forced expiratory flow at 25 % and 50 % of vital capacity, the expiratory reserve volume, and airway resistance [220]. Overall, these COPD results suggest an overall worsening of air trapping during the 30 min following the multi-technique OMT treatment in this population. In a similar COPD study testing four OMT techniques delivered separately, negative respiratory effects were again experienced with all four techniques [221]. In another COPD study, combined application of two OMT techniques (diaphragmatic manipulation and rib raising technique) over 12 weeks significantly improved ventilatory functions (VF) and functional capacity (FC), yielding better results than when each technique was delivered individually [222].

In healthy subjects, deep tissue massage resulted in a significant increase in VC and SpO2 compared to the classic massage group [223]. In another COPD study, back massage (15 min) for four days in patients while in the intensive care unit demonstrated no significant changes in systolic-diastolic blood pressures, heart rates, respiratory rate, oxygen saturation and dyspnea compared to a control (non-intervention group) [224]. In a separate single group study, women diagnosed with fibromyalgia, muscle energy technique applied to respiratory muscles resulted in significant increases in MEP, MIP and MVV compared to baseline [225]. Significant changes in arterial blood gasses (SpO2, PH and pO2) following massage therapy were reported in trauma patients [75]. Significant changes in oxygen saturation following massage were reported in liver transplant patients [79], however, other studies found no changes in oxygen saturation following massage therapy in cardiac [94] and intensive care patients [99]. However, no changes in oxygen saturation following HVL-SM were reported in normotensive [35] and hypertensive [47] adults. Using near-infrared spectroscopy (NIRS), no differences in the minimum value oxygen consumption (mO_2Hb) in the tibialis anterior was found after HVLA-SM [226].

3.4.1. Asthma

In a 2004 review of literature published between 1966 and 2002 on chiropractic care for asthma, there was no evidence that spinal manipulation should be considered as a primary treatment for asthma [227]. In a 2009 systematic review of three randomized controlled studies with excellent methodological quality, reported a lack of evidence that HVLA-SM is an effective treatment for asthma [228]. Clinical benefit of OMT for pneumonia for adults was also evaluated in a Cochrane Database Systematic Review, but limitations (including that most OMT studies were underpowered) prevented any definitive conclusions [229]. In a pre-post-test crossover design study in individuals with asthma, upper and lower thoracic forced respiratory excursion statistically increased immediately following OMT, but changes in peak expiratory flow rate changes failed to reach significance [230].

3.5. Miscellaneous ANS effects and conditions

3.5.1. Eye/pupillary effects

No changes in pupil diameter was reported in chronic neck pain participants receiving thoracic HVLA-SM [231]. However, a significant decrease in Edge Light Pupil Cycle Time, which is a measure of the pupillary light reflex, was reported in healthy participants after cervical HVLA-SM [232,233]. A significant difference in pupillary size was reported under bright illumination following cranial OMT compared to control, with both treatment and control groups demonstrating significant effects in visual acuity, local stereoacuity, pupillary size in dim illumination, and near point of convergence break and recovery [234]. In a separate study investigating the effects of osteopathic cranial manipulative treatment on visual function ($n = 89$), a statistically significant effect was observed from baseline to visit 16 in pupillary size under bright light in the left eye, and in near point of convergence break suggesting a potential impact of cranial manipulation on certain visual function parameters [235]. Much more work is needed to confirm and expand upon these early findings.

3.5.2. Otitis media

Children with otitis media receiving standard of care (SC) and three OMT visits showed statistically significant improvement in tympanogram analysis and acoustic reflectometer readings compared to SC treatment only [236]. Fewer episodes of acute otitis media were also reported in a similar study of SC + OMT vs SC only, however this study had a large dropout rate (25 %) making any definitive conclusions difficult [237].

3.6. Gland & gastric studies

In a study of salivary dysfunction and parotid gland (PG) massage (1 min; 20 applications) in thyroid cancer patients, mean radioisotope accumulation in the salivary gland was significantly lower in individuals receiving massage compared to those that did not, thereby limiting toxicity [238]. It was hypothesized that PG massage physically "milks out" the radioisotope into the oral cavity or out of the salivary duct without increasing salivary blood flow [238]. In a similar PG massage thyroid cancer clinical trial, serum amylase was significantly reduced with massage along with the incident of parotid gland abnormality at eight months following high-dose radioactive iodine therapy [239]. A separate PG massage study reported significant reductions in radioiodine uptake with one and 2 min PG massage compared to baseline, but no differences in uptake between one and 2 min PG massages [240]. In another small study ($n = 9$), OMT was demonstrated to alter gastric myoelectric activity compared to a control as well as decrease the rate of change in the frequency response to a water challenge suggesting a gastric physiological effect of treatment [241].

4. Discussion

Identifying MT-related ANS and/or viscera-related changes and their physiological underlying mechanisms is a daunting task due to the complexity, involvement, and interaction of multiple body systems during and after the delivery of any form of MT. However, with advances in today's scientific tools and technology, long-standing MT mechanism-oriented questions can be more successfully investigated given sufficient research interest and a collaborative multi-disciplinary research approach. Increased collaboration among MT researchers becomes particularly important as individual MT professions often use terminology and methodologies unique to a particular MT profession making interpretation of findings more difficult for other MT-related researchers and clinicians. The original research included in the current narrative review presents a picture of mixed evidence as to whether acute or intermediate changes in cardiovascular, sudomotor, cutaneous vasomotor and respiratory function accompany MT-related treatment. However, collectively these original research studies also provide a strong platform in which to better inform, formulate, and design more rigorous clinical mechanistic-oriented studies while taking steps to avoid weaknesses and pitfalls that are well documented in systematic reviews on this topic [5–11]. Systematic reviews of MT and ANS function, for the most part, all share a common similarity in the inability of drawing definitive conclusions primarily due to an inadequate number of studies, inconsistencies arising from profession-specific terminology, heterogenous, measures and methodology, poorly described MT interventions, and/or lack of appropriate study controls [5,11,242,243]. MT-related ANS effects may differ between asymptomatic and symptomatic populations, as well as responses between different regions of the body receiving MT treatment [5,11].

Some evidence presented in this review suggests that MT can decrease systolic blood pressure, while not altering diastolic blood pressure, however depending on whether studies were conducted in normotensive, stage 1 hypertensive, or hypertensive individuals appears to possibly influence overall conclusions. For massage, combining MT with pharmacological and/or other non-pharmacological BP interventions might be superior to MT treatment alone, but this needs confirmation. As to whether MT influences HR and HRV, similar numbers of studies appear to report positive and/or no changes following MT treatment. It is intriguing that the velocity in which massage is delivered yields significant differences in HR and LF/HF ratios, and study differences in application characteristics (such as frequency/velocity) may in fact be a major contributing factor to the mixed HR and HRV results between MT-related studies. For example, a recent study reported that three different spinal manipulation peak forces (approximating 200N, 400N, & 800N) resulted in significant differences in biomarker responses by higher spinal manipulation force [244]. Changes in skin conductance due to spinal mobilization application rate has also been demonstrated, with higher frequency application rates producing greater skin conduction changes [174], with both sympathetic and non-sympathetic mechanisms contributing to the regulation of blood flow.

Both lymphatic pump techniques and manual lymphatic drainage treatments have resulted in a myriad of reported ANS-related changes including BP, platelet counts, HRV, and other cardiovascular effects in early studies. Augmentation of regional blood flow and velocity appear to be associated with manual lymphatic drainage treatments, however these MT lymphatic studies are much too few in number to arrive at any definitive conclusions and/or to identify specific physiological mechanisms of MT interventions. MT studies reported mixed results concerning measures of pulmonary function such as FVC, FEV1, and PEF. More original research in pathological populations (i.e. COPD, asthma, cystic fibrosis, etc.) need to be conducted to help identify pulmonary functional changes and mechanisms related to MT. Combinatorial studies with MT and other therapeutic approaches may generate more positive respiratory functional changes, but future studies should be intentionally designed to identify specific physiological mechanisms responsible for any pulmonary functional improvement related to MT interventions.

Additional questions that need to be addressed include the role of contextual factors or whether the actual physical touch involved during MT delivery results in positive clinical differences regardless of specific MT technique or treatment method used. Touch as a therapeutic intervention alleviates not only somatic symptomatology but enhances psychological well-being. Touch has well defined neurophysiological responses, such as stimulating C-tactile fibers present in the skin [245]. These C-tactile fibers are part of the interoceptive system that provides moment-to-moment representation of all bodily sensations as part of the ongoing homeostatic and sensory afferent pathways of the ANS [246]. Since touch is a common denominator among all MT related treatments, we need to better understand the physiological effects of touch in clinical outcomes involving MT.

5. Conclusions

Despite many limitations and predominantly mixed results, the large body of original research included in this narrative review suggests that MT can in some instances elicit immediate effects on the ANS and/or viscera. A careful and broad interdisciplinary study of original MT-related and ANS literature is needed to better understand and identify previous MT study design flaws, specific types of MT intervention strengths and/or weaknesses in relation to ANS studies, the most appropriate methodologies, as well as to determine which specific populations are best-suited to perform future MT-related ANS studies. In addition to a re-evaluation of original MT and ANS-related research, insights gleaned from systematic reviews with regard to standardizing methodologies and mitigating potential bias will prove beneficial in future ANS and MT-related studies. Greater MT-related inter-and intra-professional collaboration and dialogue around mechanism-oriented MT research will be needed if we are to successfully arrive at definitive conclusions and/or identify direct MT-related effects on the ANS which may contribute to positive MT clinical outcomes.

CRediT authorship contribution statement

Murdi S. Alanazi: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Brian Degenhardt:** Writing – review & editing, Methodology, Data curation, Conceptualization. **G. Franklin:** Writing – review & editing, Project administration, Conceptualization. **Eric Jacobson:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Sandy Fritz:** Writing – review & editing, Conceptualization. **Norman Kettner:** Writing – review & editing, Conceptualization. **Vaclav Kremen:** Writing – review & editing, Conceptualization. **Laura Lipke:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **William R. Reed:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

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List of Abbreviations:

ANS	Autonomic Nervous System
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Disease
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in One Second
HR	Heart Rate
HRV	Heart Rate Variability
HVLA-SM	High Velocity Low Amplitude Thrust Spinal Manipulation
HF	High Frequency
ICMT	International Consortium of Manual Therapies
LF	Low Frequency
LPT	Lymphatic Pump Technique
MT	Manual Therapy
MLD	Manual Lymphatic Drainage
MIP	Maximum Inspiratory Pressure
MEP	Maximum Expiratory Pressure
MVV	Maximum Voluntary Ventilation
OMT	Osteopathic Manipulative Therapy
PEF	Peak Expiratory Flow
PG	Parotid Gland
RR	Respiratory Rate
RV	Residual Volume
RMSSD	Root Mean Square of Successive Difference
SNS	Sympathetic Nervous System
SpO2	Oxygen Saturation
SD	Standard of Care
VC	Vital Capacity

Appendix A. Supplementary data

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