Systematic Review

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The efficacy of manual therapy on HRV in those with long-standing neck pain: a systematic review

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Abstract

Objectives: Long-standing neck pain (LNP) is a clinical condition frequently encountered in the physical therapy clinic. LNP is a complex, multifactorial condition affecting multiple body systems including the autonomic nervous system (ANS). Traditionally, research on the impact of physical therapy on LNP has focused on self-report measures and pain scales. Heart rate variability (HRV) is an objective measure of the ANS, allowing for quantification of effects of treatment. This systematic review is intended to evaluate if manual therapy acutely affects heart rate variability in adults with long-standing neck pain.
Methods: Pubmed, Medline, CINAHL, Google Scholar, Web of Science, and Cochrane library were used to retrieve the randomized controlled trials for this review between the years 2010–2021. Search terms included: chronic neck pain, neck pain, cervical pain, manual therapy, mobilization, manipulation, osteopathy, osteopathic or chiropractic. Heart rate variability, HRV, heart rate variation, effects, outcomes, benefits, impacts or effectiveness.
Results: Of 139 articles located and screened, three full-text articles were selected for full qualitative synthesis, with a combined population of 112 subjects, 91 of which were female, with an average age of 33.7 ± 6.8 years for all subjects. MT techniques in three studies were statistically significant in improving HRV in people with LNP; however, techniques were differed across studies, while one study showed no benefit. The studies were found to be of high quality with PEDro scores ≥6.
Conclusions: Although no clear cause and effect relationship can be established between improvement in HRV with manual therapy, results supported the use of MT for an acute reduction in HRV. No one particular method of MT has proven superior, MT has been found to produce a statistically significant change in HRV. These HRV changes are consistent with decreased sympathetic tone and subjective pain.

Keywords: bodywork; manipulation; manual therapies; musculoskeletal manipulations; therapy.

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Introduction

Annually, individuals suffering from neck and back pain lose more than 150 million workdays, reducing productivity at an economic loss of $16 billion in the United States [1–5] with almost half lost due to employees aged 40–65 years [4]. Recent data shows that, regardless of age, North American populations, in comparison with other global regions, have experienced the greatest increases in the prevalence of neck pain [6]. Neck pain has a lifetime prevalence of 33–65 % [7] with 20 %–40 % of current cases each year, making it the 4th leading cause of disability. Furthermore, 50 % of those suffering from neck pain will develop LNP symptoms [2, 7–10].

Systematic reviews summarizing the utility of heart rate variability (HRV) for assessing autonomic nervous system (ANS) activity via the vagus nerve in those with pain [11–15] have recently come to the forefront as researchers investigate the validity of the metric as a measurement of treatment success for various conditions. Systematic reviews include those combining HRV with headache [16], fibromyalgia [17], long-standing fatigue syndrome [17, 18], and long-standing low back pain [19].

Due to the prevalence and impact of long-standing neck pain, it is necessary that effective non-pharmacological interventions are established and identified. As HRV has been established as a potentially acceptable and insightful biomarker for long-standing pain [20–22], this study aims to determine if the currently available research supports employing manual therapy to significantly impact long-standing pain through the primary outcome measure of HRV. Secondary outcomes include measures of disability, subjective pain reporting, and impact on quality of life. There is currently no systematic review that has studied these outcomes for the long-standing neck pain population. This systematic review is intended to evaluate if manual therapy affects heart rate variability in adults with long-standing neck pain.

HRV serves as a proxy for observing the interplay between the sympathetic and parasympathetic nervous system [23, 24]. Lower variability in heart rate, which is considered to be an indication of parasympathetic dysregulation, is associated with decreased post-stress recovery and increased risk of cardiovascular disease [25], long-standing pain states, fibromyalgia, complex regional pain syndrome, and phantom limb pain [26]. A large amount of variance between heart beats is optimal as it reflects the degree to which cardiac activity can be modulated to meet the varying demands of daily life [27]. Due to its potential as an objective metric for autonomic functioning, HRV may be useful for assessing treatment effects on the ANS within the clinic.

Despite the potential use of HRV to assess measurable and objective changes in the clinic, many variables can influence HRV which is not yet fully understood which include breathing rate, the experiences of physical or mental stress either from personal factors, the environment in which testing occurs, or a combination of factors [28, 29]. The potential changes in those with an altered ANS system might result in more remarkable changes than those with a more homeostatic ANS system. Furthermore, different methodologies utilizing different ANS metrics (e.g., HRV, skin conductance, skin temperature, and heart rate, to name a few) further decrease confidence in measuring this biomarker [28, 29]. Thus, it is crucial for manuscripts to clearly describe the methods and equipment used to capture HRV changes with interventional research.

It has long been considered that direct human touch, or manual therapy, can alter autonomic functioning [30]. “Manual Therapy” is defined by the American Physical Therapy Association as “a continuum of skilled passive movements that are applied at varying speeds and amplitudes, including a small amplitude/high velocity therapeutic movement” [31]. Manual therapy techniques are not inclusive to any one profession as manual techniques are utilized by osteopaths, osteopathic physicians, chiropractors, physiotherapists, massage therapists, tuina and shiatsu practitioners, to name a few. There are a wide range of therapeutic techniques on this continuum commonly employed by rehabilitation specialists aimed at affecting joints (joint mobilization and manipulation) as well as soft tissue interfacing including: skilled massage-like soft tissue mobilization techniques, myofascial release techniques, and acupressure-like trigger point release [32, 33]. Due to the wide range of commonplace techniques used in conservative management of LNP, for the purposes of this review, joint mobilization/manipulation, massage, myofascial release, and acupressure will be accepted as manual therapy interventions.

Long-Standing pain persisting three months or longer has been associated with autonomic dysfunction which contributes to increased resting heart rate and reduced HRV [26]. In many cases, long-standing pain induces an imbalance of the autonomic nervous system (ANS) in which there is increased activity of the sympathetic nervous system (SNS) and decreased activity of the parasympathetic nervous system (PNS) [34, 35]. This imbalance reduces the flexibility of the ANS adaptive response to various threats of physical or emotional pain [26] and is suspected of playing a key role in pain persistence. The imbalances are evidenced by self-reports of increased pain and disability. Because of this connection between HRV, the ANS, and long-standing conditions, it may be a reliable objective metric for assessing the health of the SNS and PNS stress response [34, 35].

As an objective indirect metric of the autonomic system, HRV is sensitive and noninvasive. Using a standard electrocardiogram (ECG), HRV measures the R-R interval, assessing for variability, or the difference between successive beats, using either time domain analysis or frequency analysis [26]. The two most common time domain measures presented in literature include normal-to-normal R-R intervals (SDNN) and the root means square of successive differences (RMSSD), both of which address short-term variability estimates and are associated with PNS response. The three most common frequency spectral analyses in the literature include high frequency (HF; 0.15–0.40 Hz) analysis, reflecting fluctuations in vagal tone, low frequency (LF; 0.04–0.15 Hz) analysis, associated with blood pressure changes and baroreflexes, and the LF/HF ratio. Although both HF and LF measure ANS activity, HF is a reflection of the PNS while LF is linked with analysis of the SNS while the LF/HF ratio is an indicator of overall sympathovagal balance of SNS and PNS [26, 33, 35–37]. An increased HRV indicates a shift toward increased PNS activity while low HRV indicates that the SNS is more dominant. Therefore, higher HRV levels and where HRV is adaptable to stress are indicative of a healthy and efficient ANS while lower HRV levels indicate a less efficient or less flexible ANS which is less stress adaptive [38, 39].

Methods

Inclusion and exclusion criteria

Inclusion criteria include:

(1) Interventional studies including randomized controlled trials, prospective cohort studies, case-control studies, retrospective studies, and cross-sectional studies of grade 3 level of evidence or higher. We will include relevant interventional studies identified in Azusa Pacific University's ProQuest libraries database.
(2) Studies on adults with long-standing or chronic neck pain >3 months duration who received manual therapy interventions.
(3) Studies that use heart rate variability as an outcome metric for those with LNP.
(4) Studies conducted in adults, 18 years of age and older.
(5) Search publication dates which are within the last from 2010 to present.

Exclusion criteria include:

(1) Publications that are greater than 10 years from search date criteria.
(2) Non-English publications.
(3) Abstracts, letters to the editor, conference proceedings, case study/series studies, commentaries or educational reviews, systematic reviews, and meta-analyses.
(4) Studies conducted on animals.
(5) Studies on specific diagnoses of fibromyalgia, long-standing headaches, persistent headaches, or acute neck pain (less than 3 months duration).

Inclusion criteria was comprehensively designed to capture all relevant literature, including unpublished (i.e., grey literature), in order to minimize reviewer bias [40]. To further limit bias, clearly defined data management strategies with specific synthesis reporting metrics, the use of quality assessment metrics, and systematically appraising for risk of bias are mitigation strategies were utilized. Research will be limited to English publications as language restrictions have been proposed to have little overall influence on publication bias [41].

While HRV has been utilized in cardiovascular research since the mid 1960s [42], recent technological advances have increased reliability of devices which are more accurate physiologic data for understanding the autonomic nervous system [42, 43]. Recent advances in HRV technology within the last decade have provided access to an increased number of reliable devices, which may be more valuable and accurate physiological data to better understand the impact of various treatment interventions on the autonomic nervous system [42, 43]. Prior research has shown applicability for HRV as an objective metric by which to measure physiological change in those with long-standing pain [44, 45] and after manual therapy intervention (e.g., Maitland mobilization grade III) [46]. Due to these advances in applied HRV and the more recent application of the technology to measure physiological function, this study will search literature within the last 10 years for applicable studies assessing the impact of manual therapy on HRV.

Despite technology advances for HRV equipment, data collection methods using HRV equipment has not been collected in a standardized manner so the reader can judge the quality of the HRV data. Picchiottino et al. [47] suggested a technical quality check list by which to score information presented which was obtained through use of technological equipment (see Table 1).

Prior research was used to determine what constitutes chronicity or long-standing symptoms of pain. These included systematic reviews and various prospective research designs defining chronic or LNP as greater than or equal to three months [22, 48–51]. Therefore, this study will define chronicity or long-standing pain as greater than or equal to three months as an inclusion criterion.

Electronic search strategy

The search was conducted using the following electronic databases (CINAHL, PubMed, Medline, Cochrane library, and Google Scholar). Search limitations included language restriction to exclude non-English publications and focus on publications from January 2011-October 18 2022. Study identification included both electronic searching strategies and manual searching. Electronic searches involved the electronic databases and search terms listed below, with specific search threads provided in Appendix A. Citations of the relevant studies for references for potential articles to be included in the review were also screened. Original authors were contacted for any missing data.

Search terms

Search terms related to participants: chronic neck pain, neck pain, cervical pain.

Search terms related to physical intervention: manual therapy, mobilization, manipulation, osteopathy, osteopathic or chiropractic. Search terms related to outcome metric: heart rate variability, HRV, heart rate variation, effects, outcomes, benefits, impacts or effectiveness.

Results

Selection procedures

The results of the literature search and study selection are shown in Figure 1. In summary, 139 records were identified after removing duplicates, non-English studies, studies in which the full text was not available and those not conducted on humans. After screening the titles and abstracts, 11 eligible studies remained, and the full-text versions for each manuscript were reviewed. Two articles were immediately excluded as one was a systematic review and the other was a protocol, leaving 9 eligible studies for full-text review. After reading the full text, 6 articles were excluded after full review: one was a protocol, one did not involve LNP patients, two included healthy subjects only, one was a systematic review, and one did not assess HRV effects acutely. Once this process was complete, only 3 articles remained that met the inclusion and exclusion criteria. Three reviewers (MS, PP, and BH) working independently screened the titles and abstracts of all studies identified

Table 1: Technical quality check-list (scoring system) [Picchiottino M, Leboeuf-Yde C, Gagey O, Hallman DM. The acute effects of joint manipulative techniques on markers of autonomic nervous system activity: a systematic review and meta-analysis of randomized sham-controlled trials. *Chiropr Man Therap*. 2019;27:17. Published 2019 Mar 12. doi:10.1186/s12998-019-0235-1].

Study ID	Treatment or intervention performed by experienced person? /1	Interventions & control procedures described? /1	(1) Was main outcome measure reported as reproducible, reliable or was it tested in study? (2) And if so, was reference correct or did own test show acceptable results? /1	Data acquisition (1) Controlled experimental conditions? (2) Was the measurement procedure described? (3) Was the duration of the stabilizing period acceptable? (4) Were measurements performed by experienced person? (5) Adequate sampling rate? /5	Data cleaning process described? /1	Was power calculation done? /1	Score	'Mechanical' profile of the sham procedure
	yes (1 point) **no or '?' (0 point)**	**yes (1 point)** **no (0 point)**	(1) **yes (0.5 point)** **no (0 point)** (2) **yes (0.5 point)** Providing at least the ICC score or equivalent **no (0 point)**	(1) Did they control one or several of the following parameters which may have an impact on autonomic measures, e.g., temperature, humidity, food/caffeine/tobacco/alcohol intakes, physical activity, breathing rate? **yes (1 point) no or '?' (0 point)** (2) **yes (1 point) no (0 point)** (3) **yes≥5 min (1 point) no<5 min or '?' (0 point)** (4) **yes (1 point) no or '?' (0 point)** (5) **yes (1 point)** For SC, ST, SBF: at least 20 Hz, 100–200 Hz is better for HRV: 1,000 Hz or higher values **no or '?' (0 point)**	Did they provide information about the visual analysis of the raw data (e.g., ECG, SC, ST, SBF)? Did they provide information about how they dealt with measurement issues (e.g., artifact correction)? **yes (1 point)** **no or '?' (0 point)**	**yes (1 point)** If the power calculation was performed for the primary autonomic outcome variable **no (0 point)** **Not applicable** If power calculation was not performed but there was a statistically significant difference between the JMT and the Sham for at least one of the main outcome variables. Or if it is a pilot/preliminary study Or if the power calculation was based on another variable		(1) **Similar to the JMT** e.g., sham mobilization performed with oscillatory movements (without the joint component)e.g., sham SNAGs performed with a sustained pressure (without the joint component)e.g., sham HVLA manipulation performed with preload and thrust phases (without the joint component) (2) **Manual contact without movement** (3) **Activator (instrument)**

Table 1: (continued)

Matsubara (2011)	**No: 0 (not described; but same investigator)**	**Yes: 1**	**No: 0 (not stated; used a standard portable ECG unit (AC301A, GMS, Tokyo, Japan)**	(1) **Yes: 1 (same time of day – afternoon)** (2) **Yes: 1** (3) **Yes: 1 (5 min)** (4) **No: 0 (not stated)** (5) **No: 0 (not stated; AC301A samples at 1,000 Hz; LF at 0.04–0.15 Hz & HF at 0.15–0.5 Hz)**	**No: 0 (not stated; used HRV data processed analysis software**)	**No: 0 (not stated)**	**4/10 40 %**	**Similar (two different regions) & control group**
Rodriguez (2021)	**Yes: 1 (manual therapists, 10 years' experience)**	**Yes: 1**	**No: 0 (not stated; used a standard device) (Polar RS800cx, Polar, Finland)**	(1) **Yes: 1 (caffeine, alcohol)** (2) **Yes: 1** (3) **Yes: 1 (10 min)** (4) **No: 0 (not stated)** (5) **Yes: 1 (Polar RS800 cx samples at 1,000 Hz)**	**No: 0 (not stated; used data processed software)**	**Yes: 1 (80 % power, 51 participants, *p*<0.5; effect size 0.4 between groups)**	**7/10 70 %**	**Instrument (placebo ultrasound as control group)**
Morikawa (2017)	**Yes: 1 (licensed acupuncturist 6 years' experience)**	**Yes: 1**	**No: 0 (not stated; used a standard device) (V5 chest leads Makin AD2, Suwa Trust, Japan)**	(1) **No: 0 (not stated)** (2) **Yes: 1** (3) **No: 0 (not stated)** (4) **Yes: 1 (licensed acupuncturist)** (5) **No: 0 (not stated; Makin AD2 system samples at 1,000 Hz; LF at 0.04–0.15 Hz & HF at 0.15–0.5 Hz)**	**No: 0 (not stated)**	**Yes: 1 (80 % power, 20 participants, *p*<0.5)**	**5/10 50 %**	**Similar to JMT (compression Non-MTrPs 2 cm & proximal to MTrP)**

The bold is the category for each column.

according to the selection criteria. Consensus was made after the initial screening review to determine which studies required a full review. Full texts will be retrieved from studies that satisfied all selection criteria for a full review. Two authors independently extracted the data and reached consensus, involving a third reviewer was not necessary. Studies were selected for retrieval following the procedure illustrated in Figure 1.

Data management

The data extracted included author, year of publication, study design, study population (i.e., diagnosis and age), interventional details, study methodology including randomization and blinding, specific parameters of HRV, number of cases (i.e., subjects), duration of follow-up, secondary outcomes such as pain and disability measures. The chart with these parameters can be found in Table 2. The authors independently completed a quality analysis via physiotherapy evidence database (PEDro) and a risk of bias (RoB 2) for each article.

Quality assessment

The Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of each study included in this systematic review. This quality assessment tool has been shown to be a valid measure to assess methodological quality in clinical trials [52]. The PEDro scale is a research quality metric to evaluate the methodology of clinical studies. The PEDro scale consists of eleven yes or no items. Although there are eleven items, the first item is representative of the study's external validity and not calculated in the total PEDro score. Thus, the score is out of a maximum of ten as the score is based on items two to eleven. PEDro scores qualify the methodological quality of studies into one of three levels: high (≥7), moderate [5, 6], or poor (0–4). For most patient care interventions, due to the impossibility of

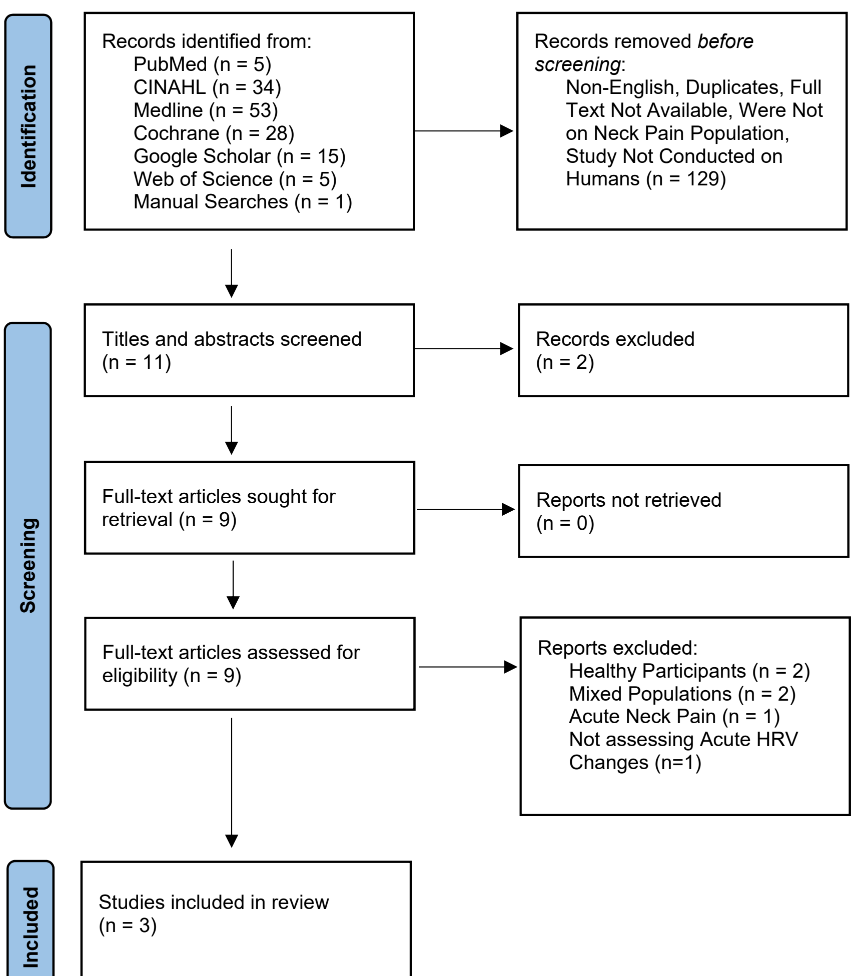

Figure 1: PRISMA flow diagram of study selection process.

Table 2: Characteristics of included studies.

Authors **Journal**	**Matsubara (2011)** **Evidenced-Based Complementary and Alternative Medicine**	**Rodriguez (2021)** **Spine**	**Morikawa (2017)** **Frontiers in Neuroscience**
Study title	*Comparative Effects of Acupressure at Local and Distal Acupuncture Points on Pain Conditions and Autonomic Function in Females with Chronic Neck Pain*	*One Session of Spinal Manipulation Improves the Cardiac Autonomic Control in Patients with Musculoskeletal Pain*	*Compression at Myofascial Trigger Point on Chronic Neck Pain Provides Pain Relief through the Prefrontal Cortex and Autonomic Nervous System: A Pilot Study*
Study design	Randomized control trial	Randomized control trial	Pilot randomized control trial
Age	33 female participants (LA group age=3 5.5 ± .4, DA group age=37.2 ± 7, control group age=34.8 ± 4).	56 Male and female participants (SM group age=40 ± 17; STM group age=48 ± 11, control group age=38 ± 13).	21 female participants age 23.4 ± 0.9
HRV outcome	Yes	Yes	Yes
Other Outcome(s)	NDI, sAA, VRS, STAI, MH	Blood pressure response to cold pressor test	Cerebral hemodynamic activity
Intervention(s)	Local acupressure (LA), distal acupressure (DA),	Spinal manipulation to upper thoracic Spine (SM) Soft tissue mobilization x 2 min (STM)	Compression of trigger point with pressure algometer attached to thumb 4 times for 30 s with 120 s in between at one session
Control group	No intervention	Placebo ultrasound	Sham compression
PEDro Score	6/10	7/10	8/10
Summary	Local acupressure sig reduced pain measures, HR and increased HF HRV	Improved HRV in SM group, no change in STM or control group, no change in CPT	LF and LF/HF ratio were significantly less in compression group; significant positive changes in subjective pain scores

NDI, neck disability index; STAI, state-trait anxiety inventory-I; sAA, salivary alpha-amylase; VRS, verbal rating scale; HR, heart rate; HRV, heart rate variability; HF, the power of high-frequency (0.15–0.4 Hz) component of HRV; LF, the power of low-frequency (0.04–0.15 Hz) component of HRV, HF/LF ratio: LF/HF ratio of HRV; SM, spinal manipulation; STM, soft tissue mobilization/myofascial release; CPT, cold pressor test; LA, local acupressure; DA, distal acupressure; MA, muscle hardness.

blinding the patient or the clinician, the maximum PEDro score for a high-quality methodological study is eight [52–55]. Two independent assessors graded each study and any variances were discussed between the three assessors. The PEDro scores for the articles in this review were overall high, with a mean score of 7/10 and a range from six to eight (Table 2).

Risk of bias

The Cochrane Risk of Bias 2 (RoB 2) tool will be used to assess risk of bias for the studies included in this systematic review. The RoB 2 is the recommended tool to assess risk of bias for Cochrane reviews [56]. Luchini et al. report the RoB2 to be the "gold standard instrument to evaluate the quality and presence of bias in RCTs" [57]. It functions by answering a series of signaling questions with; yes, probably yes, probably no, no, or no information. These answers are then interpreted through an algorithm to create a risk of bias judgement which is proposed on a scale of: low risk of bias, some concerns, and high risk of bias. There are five domains assessed with a series of signaling questions in each domain. These domains include: "1.) risk of bias arising from the randomization process, 2.) Risk of bias due to deviations from the intended interventions, 3.) risk of bias due to missing outcome data, 4.) risk of bias in measurement of the outcome, and 5.) risk of bias in selection of the reported result" [56]. Each article included in this review will be assessed using the RoB 2 by two blinded and independent assessors and any disagreement will be discussed and resolved by a third assessor.

The articles were summarized individually for risk of bias using the RoB 2 (Table 3). One study [58] had performance bias [59] and was marked high risk related to allocation concealment and non-blinding of the participants and clinicians. Two studies were given the mark of unclear in the category of "other bias" secondary to a lack of descriptive detail [58, 60] as one did not clearly define LNP [58], while another combined LNP outcomes with other long-standing musculoskeletal body regions [49]. All three studies did not blind the treating therapist [49, 58, 60].

Technical quality of HRV metric utilized in the studies

HRV measurement is a sensitive device prone to potential error leading to ANS findings that may not be clinically

Table 3: Cochrane risk of bias (RoB).

Author name, year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of assessment	Missing data	Selective reporting	Other bias
Morikawa et al., 2017	–	–	?	–	–	–	?
Matsubara et al., 2011	–	+	+	–	–	–	?
Rodriguez, et al., 2021	–	–	?	–	–	–	?

*Other bias refers to bias due to problems not covered elsewhere in the table (e.g., the study had a potential source of bias related to the specific study design used, or there is insufficient information to assess whether an important risk of bias exists, or insufficient rationale or evidence that an identified problem will introduce bias).
Green: low risk of bias (–); Yellow: unclear risk of bias (?); Red: high risk of bias (+).

relevant, even when variables are well managed and controlled. HRV may vary 30–60 % in relation to the situation, to genetic and psychosocial attributes, and to situational reaction [28, 29]. That said, HRV maintains 0.90 reliability inferring such informational variability is likely generalizable across experimental studies [28]. According to Picchiottino et al. [47], because of the potential technical ramifications of this variability in HRV, studies should provide methods detailing HRV collection and control of variables to address these points and to support the legitimacy of the findings. Each article included in this review will be assessed by two blinded and independent assessors using the technical quality evaluation proposed by Picchiottino et al. [47] and any disagreement will be discussed and resolved by a third assessor. Technical quality assessment for each article included in this study is clarified in Table 1.

Data synthesis and analysis

Systematic review

A narrative synthesis and construction of descriptive summary tables will be done for studies to describe the characterization of each study utilizing author, year of publication, study design, study population (i.e., diagnosis and age), interventional details, study methodology including randomization and blinding, specific parameters of HRV, number of cases (i.e., subjects), duration of follow-up, secondary outcome measures assessed, summary of findings. A PEDro quality scale rating, and a ROB 2 score will each be recorded in their own tables.

Meta-analysis

A meta-analysis will not be conducted as the authors of this study do not expect to identify multiple studies utilizing similar interventional study designs with pre-post analysis. Thus, there is a risk of publication, selection, and reporting bias secondary to a limited body of literature. These potential biases may result in difficulty pooling the data and may arbitrarily inflated any identified effect size. Therefore, a meta-analysis will not be completed for this systematic review. Due to the heterogeneity of the studies included in this systematic review a meta-analysis was not possible. Therefore, the data analysis was descriptive.

Characteristics of the studies

The three studies included in this review had a total of 110 subjects. Of these, 80 subjects (73 %) reported LNP as no other specific complaints other than body region was presented, while 30 subjects (27 %) served in a control/placebo group with an overall average age of 33.7 ± 6.8 years for all subjects. Those with LNP complained of various levels of reported pain, disability, and discomfort. The sample was primarily composed of female participants (n=91). The article by Rodrigues et al. [49] included other long-standing pain regions throughout the body, 15 participants ascribed to LNP. Despite this, the authors [49] make a case regarding the similarities in musculoskeletal pain regardless of body region, in regard to assessing autonomic changes. Studies took place in Japan [58, 60] and Brazil [49]. No other socio demographic characteristic information was provided from the studies. Specific demographic information was provided which included body weight [58] and body mass index [49]. One study [49] provided comorbidities which averaged about 0.09 per each group, indicating that the comorbidities identified were not meaningful and were not confounding variables to the results of the study.

All studies reported participants had LNP symptoms with Morikawa et al. [60] defining it as ≥3 months while Rodrigues et al. [49] provided a mean range between all three groups between 34 and 39 months that averaged at 37 months. Two studies listed specific exclusion criteria regarding cardiovascular disease or other cardiovascular issues [49, 58]. Matsubara et al. [58] further excluded participants if they were menstruating at the time of the data collection or were taking any type of analgesic medications. Rodrigues et al. [49] excluded participants who had consumed caffeine the day of the experiment or alcohol within the previous 24 h.

Matsubara et al. [58] had a control group but did not report that their three groups were matched despite reporting non-significant demographic differences. Rodrigues et al. [49] also had a control group. However, they failed to report if these were matched groups despite providing demographic information and identifying that all items were similar between groups except for blood pressure. Morikawa et al. [60] reported data normality using the Shapiro-Wilk test prior to statistical analysis between their two groups, which included those receiving myofascial trigger point interventions and a control group, or those who received compression at the non-myofascial trigger point region. However, they also failed to report if the control group was matched.

Outcome measures

All studies collected HRV objective biomarkers which included heart rate (HR), LF, HF, and LF/HF ratio. Heart rate variability data was collected using electrocardiogram (ECG) in three studies [58, 60] while the other used a chest heart rate monitor [49]. In addition to HRV Rodrigues et al. [49] assessed a cold pressor test as an additional ANS assessment and Matsubara et al. [58] used salivary alpha-amylase testing as a secondary ANS biomarker. Pain rating was collected using verbal rating scale (VRS) and visual analogue scale (VAS) [58, 60], and other secondary patient related outcomes were collected. These findings can be analyzed for trends in related outcomes for the purposes of this study.

Matsubara et al. [58] utilized several patient-reported outcome measures, including pain intensity using the verbal rating scale (VRS), the Neck Disability Index (NDI) to assess pain related disability, and the State-Trait Anxiety Inventory (STAI) to assess pain related to anxiety. In addition, they utilized several objective biomarkers which included salivary alpha-amylase (sAA) to measure pain-associated stress. They also assessed muscle hardness (MH) on bilateral trapezius musculature by a tissue hardness meter (PEK-1, Imoto Machinery Co. Ltd., Kyoto, Japan) pressed onto the midpoint of the Trapezius muscle between the seventh cervical vertebra and the acromion. The specific HRV measures included heart rate, HR, LF (ms^2), HF (ms^2), and LH/HF ratio. HRV metrics were collected using a portable electrocardiogram (ECG) (AC301A, GMS, Tokyo, Japan).

Morikawa et al. [60] collected pain level reports using the visual analogue scale (VAS), and a comfort or discomfort report from the procedure itself regarding the “pleasantness of the compression” which was averaged from four separate occasions. This report was collected on a −10 to +10 scale. In addition, the researchers collected perceived pain intensity score (Standard 0–10 pain where 0=No pain; 4=pain sensation at a threshold level; 10=strongest pain perception) during the compression techniques which was averaged from four separate occasions. Heart rate variability was measured by utilizing an ECG with V5 chest leads (Makin AD2; Suwa Trust, Japan) collecting heart rate (HR), LF, HF, and LH/HF ratio. In addition, cerebral hemodynamic responses in the dorsomedial prefrontal cortex (DMPFC) using near infrared spectroscopy (NIRS) were assessed.

Rodriguez et al. [49] utilized two outcome measures aimed at assessing sympathetic responses which included HRV and cold pressor test (CPT). Specific HRV measures included heart rate (HR), RMSSD, LF, HF, and LF/HF ratio and were collected using a heart rate monitor (Polar RS800cx: Polar, Finland). CPT measures included systolic and diastolic blood pressure (SBP and DBP) using a mercury sphygmomanometer (RD 202 model, Unitec, Sao Paulo, Brazil). The CPT was conducted by collecting SBP/DBP in supine, followed by submerging the non-dominant hand in cold water for up to 1 min without contracting muscles or moving the fingers. SBP/DBP were measured again 40 s after hand submersion began or at the moment the subject interrupted the test (removed their hand or made excessive movements in the water). The difference between the pre and post BP measurements was used as an index for sympathetic activation.

Main findings

Manuscripts identified for this study all used the frequency-based HRV. In general, for frequency-based HRV metrics, HF correlates to parasympathetic activity where higher HF scores are preferred. LF correlates to sympathetic activity where lower LF scores are preferred. The LF/HF ratio correlates to parasympathetic activity where lower LF/HF ratios are preferred [42]. All studies collected frequency-based HRV objective biomarkers which included LF, HF, and LF/HF ratio as indirect metrics of changes in ANS function. Each article presented the findings differently which is summarized for comparison in Table 4.

Morikawa et al. [60] identified autonomic response changes in the myofascial trigger point (MTrP) group finding significantly greater changes in HF (p<0.001) (e.g., increased HF) and LF (p<0.001) (e.g., decreased LF) with a significantly less LF/HF ratio (p<0.001) (e.g., lower LF/HF ratio) compared to the non-myofascial trigger point group (Non-MTrP). Moreover, logarithmically (ln) transformed HRV parameters were calculated with similar results where the MTrP group demonstrated significantly less lnLF (p<0.001) and lnLF/HF (p<0.001) compared to Non-MTrP. Furthermore, several correlations were identified between ANS activity and compression and subjective pain (VRS): HF% were significant and negatively correlated (r^2=0.272, $F_{(1,10)}$=7.092, p<0.05), LF% were significant and positively correlated (r^2=0.272, $F_{(1,10)}$ = 7.092, p<0.05), and the LF/HF ratio were significant and positively correlated (r^2=0.285, $F_{(1,10)}$=7.573, p<0.05). This suggests that manual compression at MTrPs significantly improved HRV homeostasis resulting in a more adaptable HRV system; thus, a healthier system.

Correlations [60] were also identified between autonomic activity and the mean effect sizes of cerebral hemodynamic responses in the dorsomedial prefrontal cortex (DMPFC) using near infrared spectroscopy (NIRS) to assess if these findings were similar to the HRV results. These findings again demonstrated improvement in HRV from manual MTrP compression: HF% were significantly

Table 4: Intervention comparison.

Authors Journal	Matsubara (2011) Evidenced-Based Complementary and Alternative Medicine	Rodriguez (2021) Spine	Morikawa (2017) Frontiers in Neuroscience
Age, n	LA group (11)=35.5 ± 6.4 DA group (11)=37.2 ± 7 Control (11)=34.8 ± 4	SM group (18)=40 ± 17 STM group (19)=48 ± 11 Control (19)=38 ± 13	MTrP group (13)=23.4 ± 0.9 Control (Non-MTrP) (10)=23.0 ± 1.0
Sex (female), n %	33 (100 %)	37 (66 %)	21 (100 %)
Time	Pre-post measures, LA and DA: 1 session of 20–25 cycles for 30 s on three points, total 90 s	Pre-post measures, 1 session of no more than 3 min duration	Pre-post measures, 8 min per compression
Intervention(s)	Local acupressure (LA): Neck/scapular muscles (GB 21; SI 14; SI l5) Distal acupressure (DA): Forearm/hand muscles (LI 4; LI 10; LI 11) Control: No treatment	Spinal manipulation to upper thoracic Spine (SM) Soft tissue mobilization (STM): Myofascial manipulation simultaneous sternum & cervical region Control (placebo): Simulated ultrasound upper thoracic spine	Compression of trigger point with pressure algometer attached to thumb 4 times for 30 s with 120 s in between at one session
HRV outcome	HF increase in LP group only[a] No change LF and LF/HF ratio all 3 groups	HF increase[a], LF and LF/HF ratio decrease[a] in SM group only	HF% increased[a], LF% and LF/HF ratio decrease[a] in MTrP group
Other Outcome(s)	No changes sAA all 3 groups Changes NDI, VRS, MH in LP group[b] Changes in STAI in LP and DA groups[b] Changes in NDI, VRS, MH in DA group[a]	No changes in blood pressure response to CPT	VRS decreased[a] in MTrP group CHA increased with Non-MTrP and decreased for the MTrP group
Correlations	N/A	N/A	HF%: sig & neg VRS LF%: sig & pos VRS LF/HF ratio: sig & pos VRS HF%: sig & neg ES CHA LF/HF: sign & pos ES CHA LF%: sign & pod ES CHA No correlation between VRS & CHA

Values expressed in means ± SD; [a]Indicates statistical significance (p<0.05); [b]Indicates statistical significance (p<0.01); CHA, cerebral hemodynamic activity; N/A, not applicable; NDI, neck disability index; STAI, state-trait anxiety inventory-I; sAA, salivary alpha-amylase; VRS, verbal rating scale; HR, heart rate; HRV, heart rate variability; HF, the power of high-frequency (0.15–0.4 Hz) component of HRV; LF, the power of low-frequency (0.04–0.15 Hz) component of HRV; HF/LF ratio, LF/HF ratio of HRV; SM, spinal manipulation; STM, soft tissue mobilization/myofascial release; CPT, cold pressor test; LA, local acupressure; DA, distal acupressure; MH, muscle hardness; sig, significant; neg, negative; pos, positive.

and negatively correlated (r^2=0.235, $F_{(1,10)}$=5.830, p<0.05), LF % were significantly and positively correlated (r^2=0.235, $F_{(1,10)}$=5.830, p<0.05), and the LF/HF ratio were significant and positively correlated (r^2=0.192, $F_{(1,10)}$=4.514, p<0.05). However, no significance was identified between VRS and effect size hemodynamic responses in the DMPFC.

Matsubara et al. [58] demonstrated that manual thumb compression to local (LP) and distal (DP) acupressure points, compared to controls, showed significant (p<0.05) changes in HF (e.g., increased HF) in the treatment performed at only the local neck musculature compared to treating the forearm and hand distal regions. No significant HRV metrics were noted in LF and LF/HF ratio for all three groups (e.g., LP, DP, and control), nor were there any sAA changes for all three groups. However, significant changes were identified at the p<0.01 level at LP for subjective pain (VRS), muscle hardness (MH), and pain associated disability (NDI). Significant changes at the p<0.01 level were identified at LP and DP for pain associated anxiety (STAI-I), while significant changes were recognized at the p<0.05 level at distal pressure points for subjective pain (VRS), muscle hardness (MH), and pain associated disability (NDI).

Rodrigues et al. [49] showed statistical significance only after spinal manipulation for changes in HF (p=0.019) (e.g., increased HF), LF (p=0.016) (e.g., decreased LF) and LF/HF ratio (p=0.029) (e.g., decreased ratio). Significance was identified for the thoracic manipulation intervention where high velocity low amplitude thrust (HVLA) consistently outperformed the myofascial manipulation (*ps*<0.03) and placebo/control (*ps*<0.04) groups with HRV changes in HF, LF, and the LF/HF ratio. The myofascial intervention and the placebo/control group did not demonstrate significance individually. Furthermore, these authors [49] found no change in their findings when outliers were removed or with age considered as a covariate.

Discussion

The results of three included studies [49, 58, 60] appears to demonstrate that manual therapy can have statistically significant impact on calming the ANS, as measured by HRV, and reducing subjective pain outcomes in populations with long-standing neck pain. Compared with controlled conditions, manual therapy interventions were associated with statistically significant [1] change in HRV consistent with decreased sympathetic tone [2], decreases in subjective pain reporting outcomes, and [3] superiority of spinal manipulation and MTrP compared to acupressure and myofascial release techniques for altering associated outcomes of pain and HRV.

There was consistency between the three studies [49, 58, 60] where manual interventions evoking acute changes in the parasympathetic nervous system (PNS). All three studies demonstrate statistically significant increases in high frequency scores (greater parasympathetic activity). Additionally, Morikawa and Rodrigues both found decreased LF/HF ratio which is considered to be a more sensitive HRV measure, than LF or HF alone. These findings are consistent with other findings which have established manual therapy alters ANS in healthy subjects using various techniques including osteopathic techniques (e.g., balance ligamentous, membranous, and cranio-sacral techniques [61], sub-occipital soft tissue mobilization [62] cervical myofascial release [63], and high velocity low amplitude (HVLA) spinal manipulative procedures [64–66].

There were statistically significant decreases in pain reporting outcomes as well as disability outcomes between the three study designs [49, 58, 60]. These findings are also consistent with prior studies that have also found significant decrease in pain outcomes associated with increased HRV [16–19]. Perhaps HRV might be useful as an objective measure to supplement the subjective pain scales currently used to assess clinical improvement from interventions towards promoting meaningful changes in quality of life and the lived pain experience.

It appears that both trigger point release techniques and high velocity low amplitude (HVLA) spinal manipulation may be more effective in evoking these PNS responses than acupressure or myofascial release. However, study design should be considered when drawing these conclusions as the implementation design for the comparators are not comparable to clinical implementation. For example, clinical myofascial release (MFR) techniques are largely personalized by clinicians based on clinical findings, vs. a standardized hand placement. Additionally, most clinicians perform soft tissue mobilization and myofascial release techniques for longer than 2 min. Standardization for study design is a common barrier in completing research on effectiveness of manual interventions [67–69].

Strengths

This study has several strengths. It is the first to review the literature on the effects of manual therapy on those suffering from long-standing neck pain using HRV as an objective metric for interventional success. All studies used industry standard equipment and validated HRV metrics of LF, HF, and LF/HF ratio as objective metrics by which to measure change in the ANS for those with LNP. Three studies [49, 58, 60] outcomes observed were statistically significant.

Limitations

This study does have several limitations. First, it is possible that gains in HRV may have been due to placebo effects rather than the interventions because the subjects were not blinded to their treatment group; however, each study attempted to control for this by measuring other ANS metrics. Matsubara et al. [58] used salivary alpha-amylase, Morikawa et al. [60] included near infrared spectroscopy, and Rodriquez et al. [49] included the cold pressor test. Second, two of the studies involved only female participants [58, 60]; however, long-standing neck pain is found predominantly in females, thus literature investigating HRV in LNP patients tends to focus on females [20, 22]. Third, two studies included in this systematic review included less commonly utilized manual therapy interventions [58, 60]. Finally, due to the small sample sizes in the three studies [49, 58, 60], and with only two providing a power analysis (see Table 1), it is difficult to draw definitive conclusion and limits the generalizability of these findings.

Another limitation of all three study designs includes time frame of follow up. All three studies look at immediate outcomes on HRV and pain, and there is no assessment of the time frame of carry over. Therefore, the common clinical critique mounted against employing manual therapy for long-standing or chronic pain populations, which is that HRV changes are transient, was not addressed in the studies reviewed as they focused solely on acute HRV changes. As future research with strong methodological controls continues to identify effective outcomes, it is important to assess length of carry over and compare to healthy populations. Furthermore, these outcomes should be compared to other clinically accepted and promoted interventions, such as therapeutic exercise [70] and pain neuroscience education [71], for long-standing pain populations.

Future research

Future research should utilize the HRV assessment procedures collectively gathered in this review to investigate more methodologically robust study designs with manual therapy interventions for those with long-standing neck pain. There is a gap in the quantity and quality of currently available research regarding manual therapy techniques for LNP. This dearth of research contributes to difficulty in drawing definitive conclusions regarding the efficacy of manual therapy. Emphasis should be placed on identifying minimal deductible change (MDC) and minimal clinically important difference (MCID) for HRV changes in order to further support what is a reliable and meaningful clinical change.

Should future research support HRV as a reliable and objective metric of ANS function, it may be useful to identify efficacious treatment interventions for those with long-standing neck pain conditions, living in a heightened sympathetic nervous system state where tolerance thresholds to various sensory input (e.g., movement, sights, sounds, situations, to name a few) is lower and less adaptable; thus, impacting the quality of life.

As HRV research develops, it would strengthen future research using HRV technology to establish a systematic method similar to that devised by Picchiottino et al. [47] and the proposed solutions provided by Roura et al. [29] to manage common issues with HRV research when developing a methodology and when presenting the data so the reader can effectively evaluate the results as many variables can influence HRV values.

Conclusions

This review found three studies [49, 58, 60] with manual therapy interventions that evoked acute changes in HRV. Such acute HRV changes directly after manual therapy treatment might indicate a temporary return to ANS homeostasis in those with LNP. As earlier identified, these study's findings are consistent with previous studies which found measurable HRV changes for various long-standing conditions [16–19, 26], using various non-manual therapy interventions (i.e., biofeedback, breathing) [72–75], and from various manual therapy interventions [61–66]. This systematic review was the first to asses research studying HRV changes in those with long-standing neck pain receiving a manual therapy intervention.

The findings of this study support further exploration of the impacts of manual therapy for non-pharmacological management and treatment of people suffering from LNP. Further research should be done exploring these techniques as part of a multi-modal approach to improve function and quality of life. Such high quality randomized clinical trials (RCTs) with control groups are necessary to establish clear and effective protocols in the treatment of LNP and to further investigate MT's effect on the ANS.

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Appendix A

CINAHL

((heart rate variability or hrv or heart rate variation) AND (chronic neck pain* or neck pain* or cervical pain*) AND (manual therapy* or mobilization* or manipulation* or massage* or osteopathy* or osteopathic* or chiropractic*)) NOT (fibromyalgia or fibromyalgia syndrome).

PubMed

(heart rate variability or hrv or heart rate variation) AND (manual therapy or mobilization or manipulation or massage) AND (outcomes or benefits or effects or impact or effectiveness) AND (chronic neck pain or neck pain or cervical pain).

Medline

(heart rate variability or hrv or heart rate variation) AND (manual therapy or mobilization or manipulation or massage) AND (outcomes or benefits or effects or impact or effectiveness) AND (chronic neck pain or neck pain or cervical pain).

Cochrane

(heart rate variability or hrv or heart rate variation) AND (manual therapy or mobilization or manipulation or massage) AND (outcomes or benefits or effects or impact or effectiveness) AND (chronic neck pain or neck pain or cervical pain).

Google Scholar

(heart rate variability or hrv or heart rate variation) AND (manual therapy or mobilization or manipulation or massage) AND (outcomes or benefits or effects or impact or effectiveness) AND (chronic neck pain or neck pain or cervical pain).

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