Heart Rate Variability in Manual Medicine

A Systematic Review

MASTER - THESIS

for obtaining the academic degree

Master of Science

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submitted by

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Abstract

***Objectives*:** To systematically investigate the effect of manual medicine approaches on the autonomic nervous system indexed by time and frequency domain measures of HRV (Heart rate variability).

Design: systematic review

Methods: 11 databases (AMED, Cochrane Library, CINAHL, PubMed, Ovid Medline, Scopus, Web of Science, ICL, OSTMED.DR, Osteopathic Research Web, PEDro) were screened for eligible studies based on pre-defined inclusion criteria. The review was performed to in accordance to PRISMA guidelines, the search was restricted to publications in English or German published up to 10/6/2018. All selected studies were evaluated with Downs-and-Black-Checklist, and one developed by the author to investigate the adherence to HRV measurement standards based on existing national and international guidelines for measurement and data extraction.

Results: 31 studies were included in the review. There is a tendency that spinal manipulation applied to the cervical and lumbar spine increases HRV and high frequency (HF) band in particular and at the thoracic spine increases low frequency (LF) band. Myofascial techniques also increase HF. For craniosacral therapy and general OMT the results are conflicting, but there is a tendency that they both increase the variability, especially RMSSD, SDNN and HF, thus having an impact on the ANS.

Discussion: The majority of the studies have moderate quality evaluated with the Downs and Black checklist. Most studies did not adhere to standards of measurement.

Conclusion: There are conflicting results from trials with small sample sizes. No general assumptions regarding the effect of OMT on the ANS can be drawn. Further research should adhere to standards of measurements and consider external and internal disturbing factors, that may influence results of HRV analysis.

***Keywords*:** autonomic nervous system – heart rate variability – manual medicine – manipulation, osteopathic – systematic review

Kurzzusammenfassung

Ziel: Nachweis der Wirksamkeit osteopathischer und manualtherapeutischer Techniken auf das autonome Nervensystem mittels Herzratenvariabilität (HRV).

Studiendesign: systematic review

Methoden: 11 Datenbanken (AMED, Cochrane Library, CINAHL, PubMed, Ovid Medline, Scopus, Web of Science, ICL, OSTMED.DR, Osteopathic Research Web, PEDro) wurden nach geeigneten Studien durchsucht. Die Suche schloss deutsche und englische Publikationen ein. Alle ausgewählten Studien wurden auf ihre Qualität mit Hilfe der Downs & Black Checklist und auf die Einhaltung von Standards der HRV Messung hin untersucht.

Resultate**:** 31 Studien, die bis zum 6.10.2018 publiziert wurden, wurden in den Review inkludiert. Es gibt eine Tendenz, dass spinale Manipulation im Bereich der Hals- und Lendenwirbelsäule die HRV und der „High Frequency“ (HF) Bereich steigert, und im Bereich der Brustwirbelsäule der „Low Frequency“ (LF) Bereich im Spektrum zunimmt. Myofasziale Techniken führen zu einer Steigerung der HF Komponente. Für craniosakrale Techniken und allgemeine OMT sind die Ergebnisse widersprüchlich, aber es besteht eine Tendenz, dass beide Behandlungstechniken ebenfalls die Variabilität steigern und somit einen Einfluss aus das ANS haben.

Diskussion: Die Mehrheit der Studien haben nur eine moderate Qualität gemessen mit der Downs & Black Checklist und setzten Standards der HRV Messung nicht um.

Fazit: Es gibt widersprüchliche Ergebnisse aus Studien mit kleinen Studienpopulationen. Es können keine generellen Aussagen zur Wirksamkeit der Osteopathie und der Manualmedizin auf das autonome Nervensystem gemacht warden. Zukünftige Forschungsprojekte sollten die Standards für die Messungen einhalten und interne und externe Störfaktoren berücksichtigen.

Schlüsselwörter: Osteopathische Medizin – manuelle Medizin - vegetatives Nervensystem – Herzratenvariabilität

Contents

1 Introduction

Osteopathic Manipulative Medicine (OMM) is a branch of manual medicine founded by Andrew Taylor Still in the United States of America in the 1890s (Still, 1897). In the United States of America, osteopathic physicians have full practice rights like their allopathic colleagues (Carreiro & Fossum, 2011). In Europe the profession still struggles to gain recognition and is to date only regulated in eight countries, but neither in Austria nor in Germany ("FORE - Forum for Osteopathic Regulation in Europe," 2018). Furthermore, in the light of exploding costs in the healthcare system, allopathic physicians, health insurance companies and government organisations alike, challenge osteopaths to provide scientific evidence for the efficacy of their treatment.

Each research project should adhere to universal standards that have already been established in medicine. Evidence based medicine has become a gold standard for selecting treatment options. Each health care practitioner is required to integrate their personal clinical experience with the best available external evidence and the goals and preferences of their individual patient to achieve an optimal treatment (Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). For this process it is crucial to be up-to-date with research in one's line of work and to be able to assess the quality of published studies. Since the internet provides a myriad of data, selecting relevant information has become crucial. A systematic review, based on a specific research question, offers a comprehensive overview of the current literature and a quantitative, and if possible, a qualitative, summary of the findings. Systematic in this context means a clearly defined process of identifying, selecting and evaluating relevant literature according to explicitly defined criteria (Antes & Bassler, 2003).

The review at hand focuses on the influence of osteopathic manipulative medicine (OMM) and other related manual treatment approaches on the autonomic nervous system (ANS) and how to measure the response of the ANS to the treatment. Osteopathic treatment approaches aim at the musculoskeletal system but are said to influence the organs, the craniosacral system and harmonize regulatory mechanisms of the body. Many diseases have their roots in stress and a reduced capacity of the body to adapt to internal or external stimuli. Therefore, the function of the autonomic nervous system plays a vital role in OMM.

Assessing the treatment effect on the ANS is not so easy, as the ANS is very complex and its reaction is highly specific. There are a number of methods to assess

ANS function. Each of them has its advantages and possible pitfalls. In the recent years heart rate variability (HRV) has become popular in research.

The aim of the review at hand is to provide a summary of current studies using HRV analysis as surrogate marker for the response of the ANS to treatment interventions in manual medicine. This work discusses HRV analysis with its potential caveats, it assesses the methodological quality of the selected trials, and provides recommendations for further research projects.

Previous reviews exist that evaluated the effect of osteopathic and manual therapy approaches on the autonomic nervous system. Jäkel & von Hauenschild (2011, 2012) assessed the effect of craniosacral therapy, the studies included in that review used multiple measurement techniques, not only HRV, to demonstrate the treatment effect. A more recent review focused on HRV in osteopathic medicine trials (Günther-Borstel, Schmidt, & Liem, 2015). The review at hand uses a wider search strategy that includes more databases and includes more recent studies and focuses on the methodological quality of the assessed studies, as methodological details of HRV analysis are required for critical evaluation.

OMM is not restricted to craniosacral techniques, treatment of the musculoskeletal system plays a vital role. Certain key regions like the cervical and thoracic spine and the sacral region are relevant if addressing autonomic structures. Treatment of the spine includes structural techniques like spinal manipulation, which is also used by chiropractors. In this line of work a number of reviews already exist. Some address changes in peripheral blood flow and sudomotor response, that are signs of altered sympathetic activity, to osteopathic or chiropractic treatment (Chu, Allen, Pawlowsky, & Smoot, 2014; Zegarra-Parodi et al., 2015). A comprehensive review by Bolton & Budgell (2012) focused on studies using spinal manipulation and measuring the effect with HRV analysis, there is a huge overlap with Swensen’s review (2011) on the same topic. However, both reviews only incorporated chiropractic studies and restricted their searches to English literature. Furthermore, a number of more recent studies were published, so there is a need to update the evidence. A more current review by Amoroso Borges, Bortolazzo, and Neto (2018) incorporates chiropractic and osteopathic studies that used myofascial techniques and spinal manipulation but not craniosacral techniques. Especially in the field of the latter, there are a number of studies which are not mentioned in the previous reviews.

The review at hand builds a bridge between osteopathic research and research in manual therapy and chiropractic respectively. While following a different philosophical approach, there still is a huge overlap in terms of applied techniques and target structures.
Previous papers in general have focused on publications in peer-reviewed journals, the work at hand also incorporates evidence from grey literature, i.e. undergraduate research, to demonstrate a broader picture of the available evidence in line with recommendations of the Cochrane Collaboration (Higgins & Green, 2011). Furthermore, a number of more recent studies on the subject demand an update of the existing evidence in a comprehensive review.

Prior to presenting the results of the review, this thesis provides background information on how manual treatment modalities can possible have modulating, regulative effects on ANS function, and why the ANS, and the vagus nerve in particular, are likely target structures for therapeutic interventions. To comprehend the relationship between ANS and pain, the role of the vagus nerve in inflammation, and psychoneuroimmunology in general, a brief anatomical and physiological background is given. In the second section HRV analysis and its usage are described.

2 Background

2.1 Autonomic Nervous System

There is growing evidence for the role of the ANS in a wide range of somatic (Martinez-Martinez, Mora, Vargas, Fuentes-Iniestra, & Martinez-Lavin, 2014) and mental diseases (Thayer, Hansen, & Johnsen, 2010).
The sympathetic nervous system (SNS) is associated with energy mobilization and is activated during stress, and the parasympathetic nervous system (PNS) is associated with vegetative and restorative functions. Under normal conditions there is a dynamic balance of both branches of the ANS. Autonomic imbalance, on the contrary, is associated with a lack of dynamic flexibility and health (Thayer et al., 2010).
The ANS together with the endocrine system control the internal milieu of the body and the maintenance of the homeostasis. Long-term processes such as body recovery, control of circadian rhythms and regulation of inflammatory processes and control of the immune system are also exercised by the ANS. By distributing specific signal generated in the central nervous system to various target organs, the ANS acts as major efferent component in this task (Jänig, 2006). The autonomic

nervous system interacts with the primitive brain, including the limbic system (serving important memory functions), brain stem and hypothalamus (Tracey, 2002).

The ANS can be divided into the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS) and the enteric nervous system (Langley, 1921). The function of the PNS is associated with growth and restoration, the SNS with the promotion of increased metabolic output necessary to deal with challenges from the environment (Porges, 2011). The PNS is defined as craniosacral system, and the SNS as thoracolumbar system, based on the specialized neuroanatomical arrangement of the outflow to the peripheral target tissues. Preganglionic nerve cells of the PNS can be found in the mesencephalon, medulla oblongata and the sacral spinal cord, those of the SNS lie in the intermediate zone of the thoracolumbar spinal cord. Each system has ganglia where the preganglionic nerve fibers synapse to the postganglionic nerve cells. These ganglia lie either prevertebrally or directly in front of the head of the ribs as paravertebral ganglia (sympathetic trunc) or close to the organ or in the wall of the organ in case of the PNS (Jänig, 2006). The “widely propagated idea of the universal antagonism between the parasympathetic and sympathetic nervous system is a misconception”, only a few target tissues receive innervation from both autonomic systems and opposite reactions to the activation are more the exception than the rule (Jänig, 2006, pos. 1314). They either work synergistically or exercise their influence under different functional conditions, their responses are coordinated to provide the appropriate internal state to meet shifts in both internal and external demands (Porges, 2011).

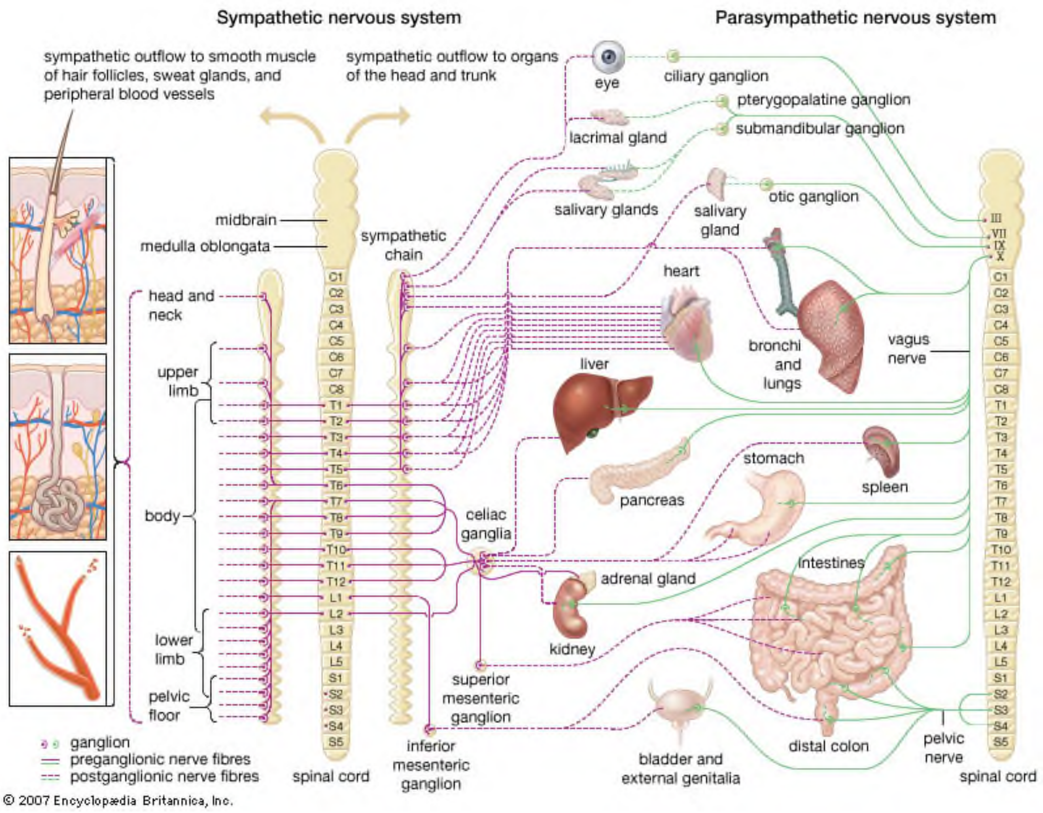

Figure 1. Overview of the autonomic nervous system

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2.1.1 Sympathetic Nervous System

The paravertebral and prevertebral sympathetic ganglia form the sympathetic trunc, a series of interconnected ganglia. At the rostral end lies the superior cervical ganglion (SCG), that contains the postganglionic neurons that project to the head and the upper three cervical segments. The stellate ganglion is a combination of the rostral upper three thoracic ganglia, it contains postganglionic neurons that project to the upper extremity and to the thoracic organs. At the caudal end the sympathetic trunci of both sides join and form the ganglion impar. Sympathetic efferent impulse reaches smooth vasculature of all organs, the heart and glands (see Figure 1). The SNS also innervates the adipose tissue, the pineal gland and lymphatic tissues. The activity of the enteric nervous system is also modulated by the SNS (Jänig, 2006).

2.1.2 Parasympathetic Nervous System

The preganglionic neurons of the PNS lie in the brain stem and in the intermediate zone of the sacral spinal cord. In the brain stem the following nuclei are considered parasympathetic: dorsal motor nucleus of the vagal nerve, nucleus ambiguus, superior and inferior salivary nuclei, visceral efferent oculomotor (Edinger-Westphal) nucleus. These preganglionic neurons project through the 3rd, 7th, 9th and the 10th cranial nerve. Pelvic organs are innervated through pelvic splanchnic nerves. In the wall or near the wall of the effector organs small ganglia can be found. The PNS innervates the exocrine glands of the head, the intraocular smooth muscles, the smooth muscles and glands of the airways and gastrointestinal tract, the pelvic organs and the epithelia and mucosa throughout the body. At the heart, the PNS innervates the pacemaker cells as well as the atrial muscle cells. The PNS is not involved in blood pressure regulation, it only innervates the helical arteries and the sinusoids of the erectile tissues and some intracranial, uterine and facial blood vessels and blood vessels in the salivary glands (Jänig, 2006). And it has immune-modulatory potential as macrophages are sensitive to PNS modulation exercised through the neurotransmitter acethylocholine (van der Zanden, Boeckxstaens, & De Jonge, 2009).

A major component of the PNS is the vagal nerve. It is important, because it transmits and integrates complex bidirectional communication between the brain and the peripheral organs involved in the cardiovascular, respiratory, digestive, and immune functions (Porges, 2011).

2.1.3 Visceral Afferent Neurons and Interoception

Afferent feedback from the body is essential to regulate the internal milieu and achieve homeostasis and adaptation to the behavior of the organism. This feedback is integrated at all levels of the autonomic motor hierarchy and projects to centers of the cerebral hemispheres that are responsible for the behavior (Jänig, 2006).

Interoceptive afferent neurons monitor physical and chemical events in the viscera, they are responsible for sensations like pain, thermal and visceral sensations like hunger, thirst, and air hunger (Craig, 2003).

Visceral organs are innervated by vagal and spinal visceral afferent neurons. They are the interface between these organs and the central nervous system, and they are involved in organ regulations, organ reflexes, neuroendocrine regulations, visceral sensations and the shaping of emotions. They monitor visceral discomfort and pain, related particular to spinal visceral afferent. Sickness behavior is generated through vagal afferents as well as neural and neuroendocrine regulation of hyperalgesia and inflammation (Jänig, 2005). They are excited by inflammation and toxic processes and may be associated with the gut-associated lymphoid tissue (GALT). Proinflammatory cytokines are able to activate vagal afferents and activate second order neurons in the nucleus tractus solitarii in the medulla oblongata which results in activation of pathways creating illness responses such as hyperalgesia and pain (Jänig, 2006).

Activity of the vagal afferents that innervate the small intestine is important in reflex modulation of inflammatory processes and mechanical hyperalgesic behavior in remote body tissues involving the sympatho-adrenal and possibly the hypothalamo-pituitary-adrenal system (Jänig, Khasar, Levine, & Miao, 2000).
About 80 - 85% of the nerve fibers in the vagal nerve are afferent (Jänig, 2006), they project viscerotopically to the nucleus tractus solitarii (NTS). The NTS is a major relay station for the neural-immune communication (Sternberg, 2006). "Ascending from the NTS, information from the vagus nerve reaches the parabrachial nucleus, the thalamus, the paraventricular nucleus, the central nucleus of the amygdala, the insula cortex, the anterior cingulate cortex (ACC) and the medial prefrontal cortex (MPFC)" (Thayer & Sternberg, 2010, p. 4). Centers involved in regulation of the autonomic nervous system, the endocrine and immune system and in behavioral regulation and emotions and in sensations like pain. These afferent neurons demonstrate a specifity with respect to the adequate mechanical or chemical stimuli. In the cardiovascular system afferent neurons can be found at the heart, ascending aorta and carotid artery. They monitor the arterial blood pressure and its changes through baroreceptors, arterial blood gases, right atrial pressure and ventricular pressure (Jänig, 2006). Animal research shows that vagal afferents, by inhibiting nociceptive impulse transmission at the level of the dorsal horn and of spinothalamic relay neurons, are able to depress nociceptive behavior if they are stimulated electrically (Randich & Gebhart, 1992). The cardiopulmonary afferents are the main inhibitors of nociceptive impulse transmission (Khasar, Miao, Jänig, & Levine, 1998). Afferent feedback from visceral organs in general often regulates PNS tone but has little impact on the SNS tone (Porges, 2011). Vagal afferent feedback plays an important role in subsequent behavioral patterns, a process labeled "neuroception", by which sensory information from the viscera and the environment is continuously non-consciously processed to evaluate risk (Porges, 2011).

2.1.4 Immunomodulation

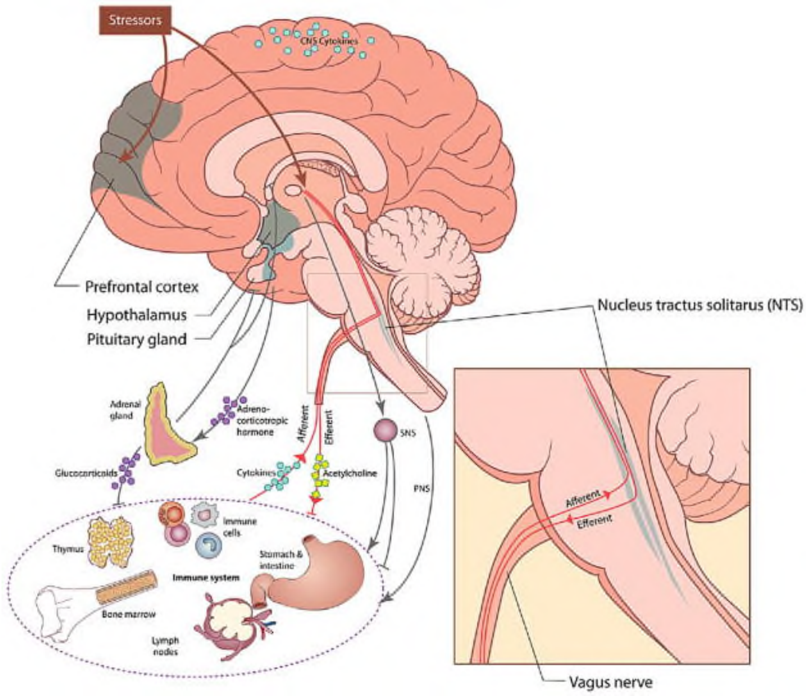

Figure 2. Neural aspects of immunomodulation

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The central nervous system and the PNS and SNS interact with the endocrine and immune system, this interaction is mediated through neurohormonal pathways involving cortisol and catecholamines and neural pathways (Sternberg, 2006). Both, SNS and PNS, are involved in this modulation of the immune system. The SNS locally controls the immune organs, including the spleen, thymus and lymph nodes, its influence can be either pro- or anti-inflammatory (Thayer & Fischer, 2009). The afferent and efferent PNS also play a role in immunomodulation (Sternberg, 2006). The connection between brain, vagus nerve and immune system has been named the "cholinergic anti-inflammatory pathway" because acetylcholine is the principle parasympathetic neurotransmitter, macrophages that are exposed to acetylcholine are effectively deactivated. Inflammatory input activates an anti-inflammatory response that is fast and subconscious (Tracey, 2002).

Cytokines are relayed through the vagus nerve to the nucleus tractus solitarii (NTS) (see Figure 2). On the efferent side, the vagus nerve innervates organs associated with the immune system such as the heart, liver and gastrointestinal tract and is able to modulate the immune activity of the spleen functionally (Thayer & Sternberg, 2010). The central nervous system inhibits macrophage activation and can decrease cytokine production via parasympathetic or vagal nerve activity (Tracey, 2002). Stimulation of the vagus nerve significantly inhibits tumor-necrosisfactor-α (TNF-α) release in liver, spleen and heart as demonstrated in animal studies (Borovikova et al., 2000).

Osteopathic treatment seems to be associated with reduction of pre-inflammatory substances (Licciardone, Kearns, Hodge, & Bergamini, 2012), hypothesizing an anti-inflammatory role of OMT (Degenhardt, Johnson, Fossum, Andicochea, & Stuart, 2017).

2.1.5 Polyvagal Theory

Current research emphasizes the importance of the vagal afferents in regulation of visceral state, mood and affect (Porges, 2011).

Porges (2011) proposed a theory, that the ANS is organized in a phylogenetic manner and that different parts of the vagal nerve have different functional properties. Each part has a different adaptive behavioral and physiological response strategy to stressful events. One branch of the vagal nerve is unmyelinated and originates in the dorsal motor nucleus and is associated with the control of the digestive system and provides low tonic influences on the heart and bronchi. The other branch is myelinated, originates in the nucleus ambiguus (NA), and is unique to mammals and provides a rapid adjustment of metabolic output by cardio inhibitory regulating heart rate via the sinoatrial node and underpins changes in HRV and approach related behaviors including social engagement (Porges, 2011).

The NA is part of the medullary network responsible for generating the respiratory rhythm, thus the output of the vagal efferents to the heart is characterized by a respiratory rhythm of increasing and decreasing tone (Porges, 1995). This rhythmic modulation is known as respiratory sinus arrhythmia (RSA), a naturally occurring rhythm in the heart rate pattern that oscillates at approximately the frequency of spontaneous breathing. By monitoring RSA, it is possible to assess the vagal output or tone of this branch of the vagus. The sinoatrial node is innervated by the branch of the vagus originating in the NA, these efferents allow a graded inhibition of the pacemaker, and this mechanism is coined “vagal brake“ (Porges, 2011). Tonic influence of the vagus is substantially lower than the intrinsic rate of the sinoatrial node. It is hypothesized that these vagal projections of the NA provide a tonic influence that promotes health, growth and restoration. When the environment is perceived as safe, it fosters calm behavioral states by inhibiting sympathetic influences to the heart and the fight-or-flight mechanisms in general and it dampens the stress response of the hypothalamic-pituitary-adrenal (HPA) axis and reduces inflammation by modulating immune reactions. Monitoring RSA in this context can serve as an index for homeostasis, stress vulnerability and reactivity (Porges, 2011).

The myelinated branch of the vagus is anatomical and neurophysical linked with the special efferents that innervate the muscles of the head and face, thus forming a so called “social engagement system“. This system is capable of dampening activation of the SNS and HPA - axis activity (Porges, 2011).

2.1.6 Model of Neurovisceral Integration

Thayer and Lane (2000) put forth the model of neurovisceral integration, it also promotes the role of the vagus, like the polyvagal theory, in inhibiting the autonomic arousal associated with affect, but it emphasizes the role of a larger neural network responsible for generating homeostatic responses, self-regulation and adaptability. The model integrates “autonomic, attentional, and affective systems into a functional and structural network“ (Thayer & Lane, 2000, p. 201). This central autonomic network (Benarroch, 1997) encompasses the medial prefrontal cortex, insular cortex, central nucleus of the amygdala, periaqueductal gray region, and the parabrachial region, and is responsible for bidirectional communication between the structures and the output regions, the ventrolateral medulla, nucleus ambiguus, and NTS. These cerebral structures tonically inhibit sympathicoexitatory circuits and the inhibition is mediated via vagal mechanisms. “This neural network can be indexed by heart rate variability (HRV), high HRV is associated with greater prefrontal inhibitory tone“ (Thayer, 2009, p. S23).

Both, “the Polyvagal theory and the model of neurovisceral integration, emphasize how reduced HRV approximates a failure to inhibit maladaptive cardiac autonomic response to stress and perceived threats, whereas increased HRV promotes behavioral adaptation and cognitive flexibility“ (Quintana, Alvares, & Heathers, 2016, p. 1).

2.1.7 Modulation of Pain

Pain can be considered as affective state which motivates behavioral disengagement from noxious stimulation (Appelhans & Luecken, 2008), it is a subjective feeling and the intensity can be dependent from the mood state (Rhudy, Williams, McCabe, & Rambo, 2005).

The dysregulation of the ANS is considered as cause for several chronic pain conditions, in these cases sympathetic influence is dominant and the influence of the PNS is decreased (Koenig, Falvay, et al., 2016). “Elevated sympathetic activity increases muscle tension and impairs local microcirculation“, which in turn leads to muscle hypoxia and increased oxidative stress. Normally, vagus nerve activity „inhibits inflammation, oxidative stress, and sympathetic activity“, it also “activates brain regions that can oppose the “pain matrix“, and it “might influence the analgesic effects of opioids“ (De Couck, Nijs, & Gidron, 2014, p.1099).

Subdiaphragmatic vagotomy leads to increase in severity and duration of pain (Weissman-Fogel, Dashkovsky, Rogowski, & Yarnitsky, 2008). Experimentally vagotomy also results in increases of adrenal medulla epinephrine (Tsutsumi et al., 2007), thus demonstrating the normally inhibitory influence of the vagus nerve on the SNS.

The effects of vagal afferent neurons on inflammation, pain and emotion are nowadays used in a treatment protocol involving transcutaneous electrical stimulation of the vagus. The vagus nerve stimulation (VNS) experimentally reduces induced pain by modulating descending serotonergic and noradrenic neurons (Kirchner, Birklein, Stefan, & Handwerker, 2000) and is used in patients suffering from migraine (Goadsby, Grosberg, Mauskop, Cady, & Simmons, 2014) and in depressive patients (Martin & Martín-Sánchez, 2012). In the latter group, this leads to cardiovascular responses demonstrated by changes in HRV (Sperling et al., 2010).

Manual medicine approaches are believed to use the same mechanisms as VNS and also have an effect on the endorphine system (McPartland et al., 2005).

2.1.8 Methods of Evaluation of ANS Function

Multiple tests assess ANS function mainly by evaluating the cardiovascular reflexes triggered through various provocative maneuvers. Due to the complexity of the ANS no single test can precisely reflect function of a specific branch of this system. Normally, a battery of tests are applied to evaluate ANS function (Zygmunt & Stanczyk, 2010).

2.2 HRV Analysis

“Analysis of heart rate variability has nowadays become one of the most popular methods for ANS evaluation” (Zygmunt & Stanczyk, 2010, p. 15). However, there is no gold standard to evaluate the ANS, and it is rather arguable whether there are evaluation methods that can display the real situation of the ANS (Ernst, 2014). Heart rate variability is the “conventionally accepted term to describe variations of both instantaneous heart rate and RR (NN) intervals” (p. 354), i.e. distance between consecutive R pikes of QRS complex in ECG recording (Malik et al., 1996) (see Figure 3).

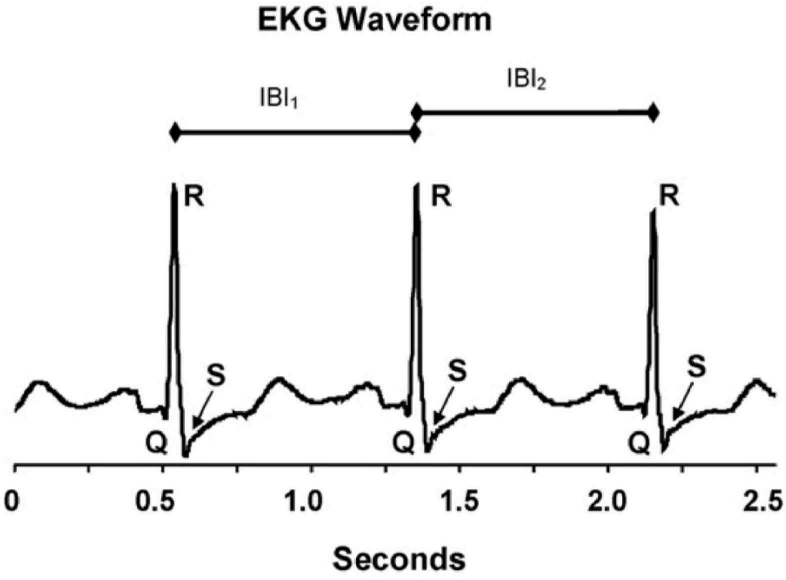

Figure 3. Illustration of interbeat intervals (IBIs) and the electrocardiogram (EKG) waveform

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HRV is a qualitative marker for the activity of the autonomic nervous system and offers insights on cardiovascular regulation mechanisms. The term HRV stands for a multitude of arithmetic parameters that display the variance, variability and complexity of consecutive heart beats (Sammito et al., 2014). HRV "reflects the heart's ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli" (Rajendra Acharya, Joseph, Kannathal, Lim, & Suri, 2006, p. 1031).

These temporal beat-to-beat changes reflect the output of a central autonomic network that directly regulates the heart and guides flexible control over behavior. HRV is also a marker for one's capacity for self-regulation, social engagement and psychological flexibility, changes in HRV occur during different emotions and mood states (Kemp & Quintana, 2013). According to the polyvagal theory, HRV is associated with the experience and expression of social and emotional behavior (Porges, 2011). Thus, HRV, though being a measure of the interplay of autonomic, humoral, and intrinsic influences on heart rate, can also serve as objective index of emotionality. HRV provides information about the ability of the nervous system to organize an affective homeostatic response in accordance with situational demands (Appelhans & Luecken, 2006).

Standards of measurements of HRV analysis were first defined in 1996 by the Task Force of The European Society of Cardiology and The North American Society of

Pacing and Electrophysiology (Malik et al., 1996) in a guideline that is still valid till this date, even though technical improvement and the development of new measurement devices have since then progressed rapidly and the normative values for healthy individuals may be outdated (Nunan, Sandercock, & Brodie, 2010).
HRV is a physiological parameter that has become widely used in cardiology, intensive-care, endocrinology, psychology, neurology, and sports medicine due to the non-invasive nature of measurement and comfortable ways of data analysis (Sammito et al., 2014).
A myriad of studies incorporates HRV analysis, the number of published studies increased immensely during the last two decades (see Figure 4).

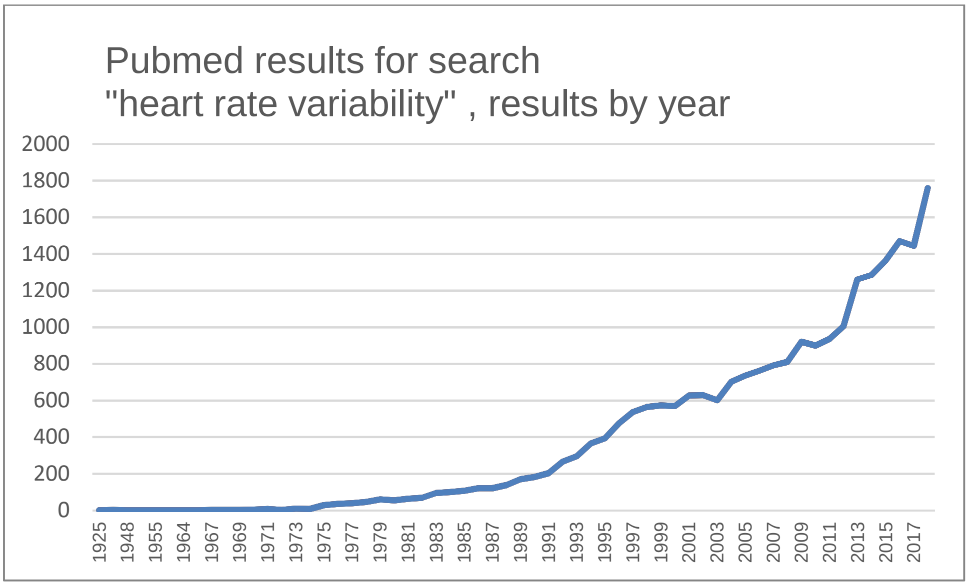

Figure 4. PubMed - Search "heart rate variability"

Data retrieved from PubMed, date of access: 31.12.2018. Graphic designed by author.

2.2.1 Physiological Mechanisms

The heart is dually innervated by the PNS and SNS. Modulation of heart rate is a means of cardiovascular control. Heart rate adapts to demands of the environment and even at rest is submitted to a physiological variability. This variability demonstrates the interaction of the sympathetic and parasympathetic nervous system. Sympathetic activation reduces HRV through release of noradrenaline, while parasympathetic activity enhances HRV through the release of acetylcholine. While they not simply act as counterparts, SNS and PNS influence HRV differently. At rest, parasympathetic influence is dominant, which leads to higher variability, this influence also produces a lower heart rate and shows itself in the sinus arrhythmia. This vagal resting tone also depends on fitness level and is increased in athletes who train in endurance sports (Sammito et al., 2014). “PNS modulation of the heart rate is fast (timescale of milliseconds), while SNS effects are slower on a timescale of seconds, the recording and analysis the sequence of intervals between adjacent heartbeats is therefore the basis of the calculation of all measures of HRV“ (Koenig, Falvay, et al., 2016, p. E3). SNS input seems too slow to alter beat-to-beat variations, a vagal dominance in creating HRV is proposed (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). “During the evaluation of HRV indices, one must realize that they are not direct indices of a tonic activity of the SNS and PNS, but rather the resultant of their influence on the effectors, which are the receptors of the sinus node cells“ (Zygmunt & Stanczyk, 2010, p. 15).

2.2.2 Metrics of HRV

Numerous methods of HRV analysis exist, but they fall mainly under three main categories: time domain, frequency domain and non-linear measures. “Time domain indices are directly derived from the R-R interval series while frequency domain measures submit the inter-beat-interval to spectral analysis and quantify power spectral density within pre-specified frequency bands“ (Koenig, Falvay, et al., 2016, p. E5). RSA, RMSSD and HF power are closely related and all reflect vagal influence (Thayer, Åhs, Fredrikson, Sollers Iii, & Wager, 2012). No single measure exists that has been hailed as gold standard (Allen et al., 2007).

2.2.2.1 Time Domain Indices

2.2.2.1.1 Statistical Methods

Time domain metrics based directly on interbeat intervals do not distinguish between the autonomic sources of the variability. These indices include the standard deviation of the average of N-N (normal to normal) intervals (SDNN), and the standard deviation of the average N-N interval for each 5 min. period over 24 h. (SDANN) (Thayer et al., 2010). The second type of time domain measures is based on differences between successive N-N intervals, these measures include the pNN50 (percentage of adjacent cycles that are > 50 ms apart) and the RMSSD (root mean square successive differences in milliseconds).

SDNN has been recommended as a measure for overall variability (Malik et al., 1996), the recording length is standardized to 5 minutes or to 24 hour long-term recordings to allow comparisons between studies (Allen et al., 2007). Variances mathematically equal the total power of spectral analysis, therefore, SDNN reflects all cyclic components responsible for variability (Malik et al., 1996).

The RMSSD is the most common time domain measure, it reflects mainly parasympathetic influence (Thayer et al., 2010). Time domain metrics have the widest application in routine clinical evaluation (Zygmunt & Stanczyk, 2010), they can be

applied secondary to respiration, tilt, Valsalva or to phenylephrine infusion (Malik et al., 1996).
RMSSD, pNN50, NN50 estimate the high frequency variations in heart rate and are highly correlated. As RMSSD has better statistical properties, this method is preferred to the other two (Malik et al., 1996).

2.2.2.1.2 Geometrical Methods

The series of NN intervals can also be converted into a geometric pattern, such as the sample density distribution of NN interval duration, and Lorenz plot of RR intervals (Malik et al., 1996). Geometrical methods present RR intervals in geometric patterns. “The triangular index is a measure, where the length of RR intervals serves as the x-axis of the plot and number of each RR interval length serves as the y-axis. The length of the base of the triangle is used and approximated by the main peak of the RR interval frequency distribution diagram. The triangular interpolation of NN interval histogram (TINN) is the baseline width of the distribution measured as a base of a triangle, approximating the NN interval distribution (the minimum of HRV). The triangular index has a high correlation with SDNN but is highly insensitive to artifacts and ectopic beats“ (Rajendra Acharya et al., 2006, p. 1037).

2.2.2.2 Frequency Domain Indices

Analysis of frequency domain can be obtain by Fast-Fourier Transformation (FFT), Autoregression (AR) (see Figure 5), Zero-crossing method, wavelet- analysis, and trigonomic regressive spectral analysis (Sammito et al., 2014).
Frequency domain analysis gives information about the amount of variance or power in the heart rate or heart period time series explained by periodic oscillations at various frequencies. Power spectral analysis provides basic information on the amount of variance or power as a function of frequency (Malik et al., 1996).
“Spectral analysis does not express heart rate as a function of time but as a function of frequency. The frequency and magnitude of these oscillations are measured“ (Zygmunt & Stanczyk, 2010, p. 15).
Four frequency bands can be distinguished from 24 h. – recordings: high frequency (HF; 0.15 – 0.4 Hz), low frequency (LF; 0.04 – 0.15 Hz), very low frequency (VLF; 0.003 -0.04 Hz), and ultra low frequency (ULF; ≤ 0.003 Hz). Only HF and LF frequency bands can be analyzed from short-term measurements (Thayer et al., 2010).

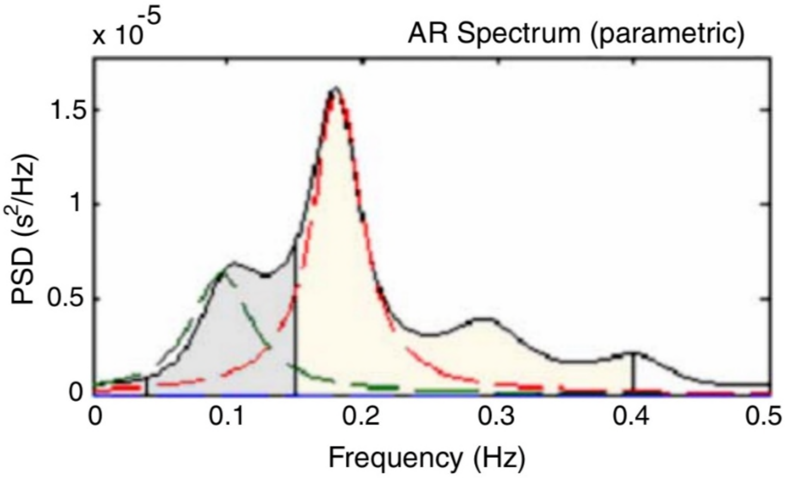

Figure 5. AR spectrum of heart rate signal

Reprint with permission from Rajendra Acharya et al. (2006).

The high frequency component (HF) is attributed to the PNS, while the LF (low frequency) component shows the influence of both PNS and SNS activity (Koenig, Falvay, et al., 2016). A linear relation of the area of the HF component and cardiac vagal tone, that was obtained pharmacologically, has been demonstrated (Hayano et al., 1991).

The ULF band has shown strong relationships with prediction of morbidity and mortality (Thayer et al., 2010). The physiological origins of the VLF band are unclear, a link with fluctuations in the renin-angiotensin system and with thermoregulation is proposed (Thayer et al., 2010).

The LF band is associated with baroreflex-mediated blood pressure variations. Supine LF power reflects baroreflex function and is thus primarily of vagal origin (Thayer et al., 2010). The HF band is parasympathetically mediated and reflects the respiration-mediated HRV (Saul, Rea, Eckberg, Berger, & Cohen, 1990), this measure highly correlates with RMSSD. HF corresponds with variations related to the respiratory cycle. These changes are known as respiratory sinus arrhythmia (RSA). “Heart rate accelerates during inspiration and slows during expiration. During inhalation, the cardiovascular center inhibits vagal outflow resulting in speeding of the heart rate“ (Shaffer, McCraty, & Zerr, 2014, p. 9). The magnitude of the oscillation can usually be exaggerated by slow deep breathing (Shaffer, McCraty, & Zerr, 2014).

The LF/HF ratio has been proposed to reflect sympathovagal balance, but this is a misconception. As Thayer et al. (2010) stated “vagal influences cover a full range of frequencies, whereas sympathetic influences roll-off at about 0.15 Hz. Thus, any measure derived from HRV analyses will have at least some parasympathetic influence“ (p. 735). And that LF/HF ratio only “reflects the relative relationship among autonomic influences“ (p. 735) and does not reflect sympathetic activity per se and should therefore be used with caution. Goldstein, Bentho, Park, and Sharabi (2011) agree that LF power is an index for baroreflex function, they argue that LF power is not an index of sympathetic outflow, because there is no correlation between values of LF and LF/HF ratio to the gold standard index of sympathetic outflow, the norepinephrine spillover, and that “drugs that increase release of norepinephrine, increase LF power even in patients with evidence of cardiac sympathetic denervation, and that blockade of preganglionic cardiac sympathetic outflow by segmental spinal anesthesia does not affect LF power“ (p. 2). Eckberg (1997) also proclaimed that vagal contributions to baseline LF RR-interval fluctuations are great, and there is evidence that baseline LF RR-interval spectral power, related quantitatively to sympathetic-cardiac nerve traffic, is nonexistent. LF power should not be used as index of cardiac sympathetic regulation (Billman, 2011, 2013), and LF/HF ratio does not display “sympathovagal balance“ (Billman, 2013). “Many studies have noted increases in LF/HF ratios and normalized LF power during orthostasis. HF power usually decreases, but LF power considered alone does not consistently increase with orthostasis“ (Goldstein et al., 2011, p. 4). During laboratory psychological challenges cardiac spillover of norepinephrine increase, indicating increased sympathoneural outflow, however, “without adjustment for HF power, LF power does not increase during laboratory psychological challenges“ (Goldstein et al., 2011, p. 4).

2.2.2.3 Non-linear Methods

Various nonlinear methods exist: Poincaré plot, multiscale entropy, approximate entropy (ApEN), sample entropy, correlation dimension, detrended fluctuation analysis, and recurrence plot analysis. Recent development in the theory of non - linear dynamics have paved the way for analyzing signals from non - linear living subjects. The non - linear dynamical techniques are based on chaos and have been applied in many areas including medicine (Joseph et al., 2004).

2.2.2.3.1 Poincaré Plot

“The Poincaré plot [geometry] is a technique taken from non - linear dynamics and portrays the nature of RR interval fluctuations. It is a plot in which each RR interval is plotted as a function of the previous RR interval. Poincaré plot is an emerging quantitative-visual technique, whereby the shape of the plot is categorized into functional classes“ (Rajendra Acharya et al., 2006, p. 1037). A common way to describe the Poincaré plot geometry is to fit an ellipse to the graph (Brennan, Palaniswami, & Kamen, 2001) (see Figure 6). "The ellipse is fitted onto the so-called line-of-identity at 45° to the normal axis. The standard deviation of the points perpendicular to this line denoted by SD1 describes short-term variability which is mainly caused by RSA. The standard deviation along the line-of-identity denoted by SD2 describes long-term variability", (p. 42-43) °a decrease in SD2 shows an increase in the trend towards chaos […], physiologically a good sign" (Joseph et al., 2004, p. 44).

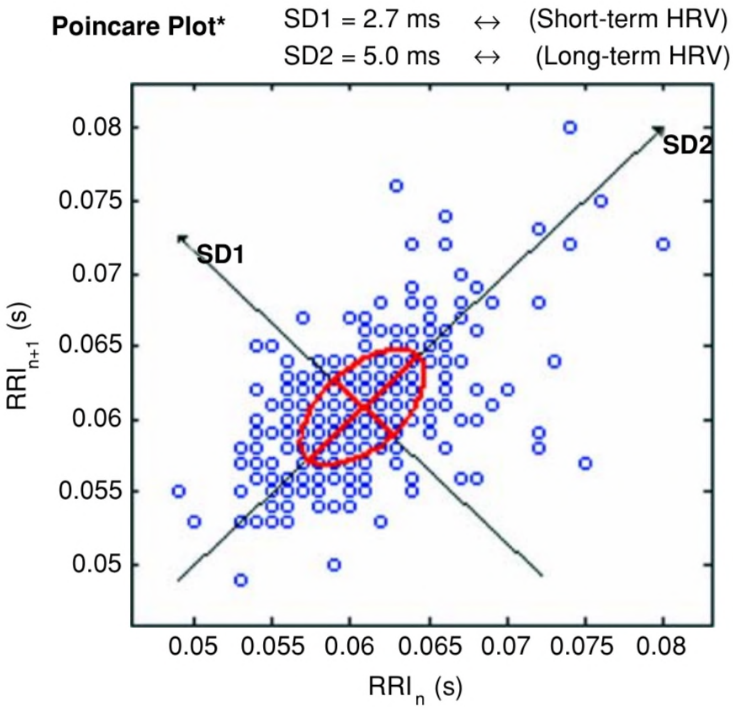

Figure 6. Poincaré plot of a normal subject

Reprint with permission from Rajendra Acharya et al. (2006).

2.2.2.4 Detrended Fluctuation Analysis

According to Rajendra Acharya et al. (2006) "the Detrended Fluctuation Analysis (DFA) is used to quantify the fractal scaling properties of short interval RR interval signals. This technique is a modification of root-mean-square analysis of random walks applied to nonstationary signals. The root-mean-square fluctuation of an integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log-log scale. […] The fractal scaling (DFAα) for normal subjects is closer to 1, and this value falls in different ranges for various types of cardiac abnormalities" (p. 1042).

2.2.2.5 Autochronic Image

Moser established an additional method to analyze HRV, he conducted 24 - hour recordings and displayed the results as time-variant spectrogram. This method visualizes rhythms of HRV in an autochronic image (see Figure 7) that is a portrait of the rhythms modulating and moving the beat of the heart. The autochronic image is used in projects of occupational health promotion, shift work and even in space medicine to diagnose sleep quality and rhythm disturbances (Moser, Fruhwirth, & Kenner, 2008).

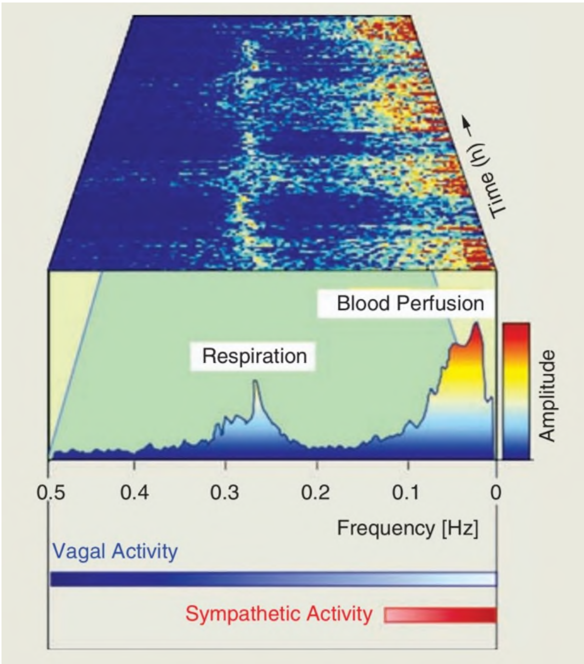

Figure 7. Time-variant spectrogram of a multi-oscillatory biological rhythm (HRV)

Reprint with permission from Moser et al. (2008)

2.2.3 Pathophysiology and Applications of HRV Analysis

“Low HRV has been proposed as a marker for disease“ (p. 225), all-cause morbidity and mortality (Thayer & Lane, 2007) and this reduction of vagally mediated cardiovascular control serves to dis-inhibit sympathoexcitatory influences (Thayer & Lane, 2000). HRV analysis is an established tool in cardiology research and is most used in surveillance of post infarction and diabetic patients (Rajendra Acharya et al., 2006). HRV can also be affected by renal failure, essential hypertension, cardiac disorders, coronary artery disease, and intracranial lesions (Litscher, He, Yi, & Wang, 2014). Aberrations from normal values of HRV are common in patients suffering from pain (Koenig, Falvay, et al., 2016; Koenig et al., 2015). Patients with functional somatic disorders are frequently searching help in osteopathic care, they also suffer from a sympathovagal imbalance that express changes in HRV due to their pain, ongoing inflammation and chronic stress responses. Fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome are examples of this entity (Martinez-Martinez et al., 2014). Parasympathetic control and afferent feedback play a vital role in the digestive system, this explains alterations in patients with irritable bowel syndrome (Chalaye et al., 2012; van der Zanden et al., 2009). Patients with systemic disorders like metabolic syndrome also present with reduced HRV (Koskinen et al., 2009). These changes in the sympathovagal balance appear also patients with psychiatric disorders like anxiety (Miu, Heilman, & Miclea, 2009) and depression (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Kemp et al., 2010; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016).

In healthy inviduals there is a relationship between HRV and social cognition. Increased resting HRV is associated with better subsequent emotion recognition (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012), an important facet of social communication, missing in children suffering from autism spectrum disorders. Individuals with low HRV are unable to suppress SNS function, leading to a mobilised behavioral state and negative affect which adversely impacts on social engagement (Kemp & Quintana, 2013).

Increased HRV is associated with various indices of psychological wellbeing, including cheerfulness and calmness (Geisler, Vennewald, Kubiak, & Weber, 2010), and motivation for social engagement (Kemp, Quintana, Kuhnert, et al., 2012). Reduced HRV, in contrast, is associated with cognitive and affective dysregulation and poorer resilience (Kashdan & Rottenberg, 2010).

Emotions show themselves in alterations of HRV and it can serve as index for of regulation or dysregulation of emotion (Koenig, Falvay, et al., 2016). Under stimulus conditions (happiness, sadness, and disgust) Lane et al. (2009) found significant covariation of increased high-frequency HRV with increased activity in areas associated with emotion: the right superior prefrontal, right dorsolateral prefrontal and right parietal cortex and the left anterior cingulate. These structures regulate vagal tone during emotion. Individuals with greater emotion regulation have greater levels of resting HRV (Appelhans & Luecken, 2006). Individuals with low resting HRV show delayed recovery from psychological stressors of cardiovascular, endocrine, and immune responses compared with individuals with higher levels of resting HRV (Weber et al., 2010).

Vagal activity, as already discussed, plays an important role in regulation of a variety of allostatic processes including inflammatory processes, glucose regulation and HPA function (Thayer & Sternberg, 2010).

Structures associated with the cardio-vagal control seem to be also involved in immunomodulation. Ohira et al. (2009) demonstrated that HRV is positively associated with the activity of the medial prefrontal cortex and the anterior cingulate cortex. A meta-analysis showed that the amygdala and insula are also positively associated with HRV in studies that measured cerebral blood flow and HRV (Thayer & Sternberg, 2010). A review (Haensel, Mills, Nelesen, Ziegler, & Dimsdale, 2008) found an inverse association between measures of HRV and inflammatory markers in healthy individuals and in those with cardiovascular diseases.

Another study described the correlation between C-reactive protein and white blood cell counts as marker for inflammation and HRV. Measures for vagally mediated HRV like RMSSD and pNN50 remained significantly inversely related to the latter (Thayer & Fischer, 2009). Various other studies demonstrated associations between low frequency spectral power and inflammatory markers (Thayer & Sternberg, 2010).

Weber et al. (2010) assessed the influence of vagally mediated HRV on the cardiovascular, endocrine, and immune systems during recovery form acute mental stress. It has been demonstrated that low HRV leads to delayed recovery of diastolic blood pressure, cortisol, and TNF-alpha up to an hour after the stressor has ended. Research showed that vagal function is important during acute and chronic inflammation (Thayer & Sternberg, 2010). A larger study with 1255 participants provided further support for the anti-inflammatory role of the vagus nerve, HF-HRV was significantly and inversely related to several inflammatory markers (fibrinogen, soluble IL-6 receptor, ICAM and IL-6) after controlling for relevant covariates (Cooper et al., 2015).

Decreased vagal function and HRV have been associated with increased fasting glucose and glycated hemoglobin (HbA_{1c}) levels, and with increased overnight urinary cortisol. These factors are associated with poor health and increased allostatic load (Thayer & Sternberg, 2006).

To summarize all applications of HRV analysis, the same research group (Thayer et al., 2012) suggested that HRV is not simply a cardiovascular marker, but may serve as index for a „super – system that integrates the activity in perceptual, motor, interoceptive, and memory systems into gestalt representations of situations and likely adaptive responses“ (p. 748), thus reflecting the activity of a complex adaptive response of the individual to function in a complex environment. High HRV is associated with high flexibility and adaptability to response to changes within the internal or external environment and therefore serves as marker for stress, resilience, context - based control of emotions and self - regulatory ability (Thayer et al., 2012).

“Deep - paced breathing relaxation has been shown to increase vagal nerve activity“ (De Couck et al., 2014, p. 1103). One form is HRV biofeedback, where patients receive visual feedback concerning their HRV. This form of biofeedback is widely used (Cowan, Kogan, Burr, Hendershot, & Buchanan, 1990; Gevirtz, 2013), for treatment of COPD (Giardino, Chan, & Borson, 2004), in functional somatic disorders like irritable bowel syndrome (Stern, Guiles, & Gevirtz, 2014), and fibromyalgia (Hassett et al., 2007), as well as in sports medicine and rehabilitation (Prinsloo, Rauch, & Derman, 2014), and for the treatment of psychiatric disorders such as anxiety (Prinsloo, Derman, Lambert, & Rauch, 2013), and depression (Siepmann et al., 2008).

A few complementary alternative treatment approaches like yoga (Lin, Huang, Shiu, & Yeh, 2015; Posadzki, Kuzdzal, Lee, & Ernst, 2015), acupuncture (Chung, Yan, & Zhang, 2014), and Reiki (Diaz-Rodriguez et al., 2011) already incorporate HRV analysis in researching their treatment effects. In massage therapy there is also an increasing number of publications on the subject (Buttagat, Eungpinichpong, Chatchawan, & Kharmwan, 2011; Diego & Field, 2009; Hatayama, Kitamura, Tamura, Nagano, & Ohnuki, 2008; Lindgren et al., 2013).

The usage of HRV analysis in manual medicine is the scope of the review at hand.

2.3 Manual Medicine

2.3.1 Manual Therapy, Chiropractic Medicine

Osteopathy, manual therapy and chiropractic medicine can be summarized as manual medicine approaches. They are very similar regarding their techniques, and during their history there are certain overlaps. Techniques from one discipline were integrated in the treatment approach of the others and there was a constant co - development over the years. Chiropractic medicine is said to derive from OMM (Lewis, 2012), and manual therapy, a form of treatment in the field of physical therapy, also has its roots in OMM (Pettman, 2007).

2.3.2 Osteopathy

OMM is a health- oriented, patient-centered approach that focuses on the "restoration, enhancement, and maintenance of normal physiological functions" (Seffinger et al., 2011, p. 4) Five basic integrative and coordinated body functions and their coping strategies and adaptations are essential for the adaptation of the body to different demands and environmental stressors, e.g. trauma, infection, nutrition and social.

- *"Posture and motion, including structural and biomechanical reliability.*
- *Gross and cellular respiratory and circulatory factors.*
- *Neurologic integration, including central, peripheral, autonomic, neuroendocrine, neurocirculatory, and their reflex relationships.*
- *Metabolic processes of all types, including endocrine-mediated, immune-regulatory, and nutritionally related biochemical processes*
- *Psychosocial, cultural, behavioral, and spiritual elements."*

  (Seffinger et al., 2011, p. 4)

These five systems or models are used in the assessment and treatment, each of them is interrelated with the others. The effect osteopathic manipulative treatment (OMT) is believed to be not limited to the musculoskeletal system. Although it is often regarded as entry point to the patient, OMT is supposed to have an impact on all the other systems as well through modulating of afferent input of the nervous system and especially through the ANS (Seffinger et al., 2011).

Treatment of certain key areas of the body is considered to have an effect on the ANS, several textbooks describe relevant techniques (DeStefano, 2011; DiGiovanna, Schiowitz, & Dowling, 2005; Kuchera, 2005; Kuchera & Kuchera, 1994; Parsons & Marcer, 2006; Seffinger & Hruby, 2007). Craniosacral techniques are said to modulate the vagal nerve through afferent feedback. Techniques that target the thoracic spine and ribs are believed to influence the sympathetic ganglionic chain. Even direct techniques on the vagal nerve are described (Barral & Croibier, 2009, 2011).

Systemic dysfunctions, infections e.g. pneumonia (Noll, Shores, Gamber, Herron, & Swift, 2000), congesting ear effusion (Steele, Viola, Burns, & Carreiro, 2010), functional organic dysfunctions of the cardiovascular system or others are proposed to be treated by the OMM approach as well (Kuchera & Kuchera, 1994).

Research on the impact of OMM on other body systems such as the ANS is nearly as old as the profession itself. Louisa Burns (1907) did basic research on neurophysiological aspects of the somato-visceral reflexes. Northup (1945) early on described the impact of manipulative techniques on the ANS and already in 1948

Waitley discussed stress theories with attention to OMM. Thorpe (1973) described the influence of OMT on the endocrinological level.

In recent years several studies assessed the effect of OMT on the cardiovascular system by measuring heart rate and blood pressure, on the endocrine system by measuring biomarkers and on the psychological system by using certain specific questionnaires. OMT is proposed to alter peripheral skin conductance and skin temperature (Chu et al., 2014; Zegarra-Parodi et al., 2015). An effect on hypertension after cervical manipulation is described (Galindez-Ibarbengoetxea et al., 2017; Mangum, Partna, & Vavrek, 2012), and OMT may play a role in the long-term treatment of hypertension (Cerritelli et al., 2011; Spiegel, Capobianco, Kruger, & Spinner, 2003). OMT has reduced pain and an increase of β-endorphin, N-palmitoylethanolamide, and anandamide, an endocannabinoid, was observed after treatment (Degenhardt et al., 2007)

In a review Jäkel & Hauenschild (2011) assessed the effect of craniosacral techniques on “pain, quality of life, sleeping habits, gross motor function and autonomic nervous system function“ (p. 685). They found that craniosacral osteopathy reduces pain in tension type-headache (Hanten et al., 1999) and improves sleep quality (Cutler, Holland, Stupski, Gamber, & Smith, 2005; Hayden & Mullinger, 2006; Wyatt et al., 2011). Alteration in ANS functions could be demonstrated in two studies regarding blood flow velocity (Nelson, Sergueef, & Glonek, 2006; Sergueef, Nelson, & Glonek, 2002). A recent article by Günther-Borstel et al. (2015), that reviewed other studies using HRV as means to demonstrate effects of OMT on ANS function, found a positive influence on HRV. Moreover, OMT seems to be associated with a reduction of pro-inflammatory substances (Licciardone et al., 2012). Osteopathic interventions, therefore, could reduce the release of cytokines and the sympathetic activity creating a cascade of biological and neurological events that modulate inflammatory and ANS mechanisms. Touch based manual practices, particularly OMT, seem to produce anti-inflammatory and hyper-parasympathetic effects and can therefore modify temporary or permanent sensitization states throughout the interaction or treatment of the peripheral tissues (D'alessandro, Cerritelli, & Cortelli, 2016).

A chiropractic review (Bolton & Budgell, 2012) also concludes that spinal manipulation has effects on HRV and therefore on the ANS.

The following review brings the evidence on the effect of spinal manipulation, craniosacral therapy and myofascial techniques up to date.

3 Methods

3.1 Study Design

The study at hand is a systematic review.

3.2 Study Aim

The study at hand focused on the usage of heart rate variability analysis to assess the effect of manual medicine approaches on the ANS. The aim of the review was to demonstrate the up-to-date state of research on this topic. The selected studies were assessed in terms of their methodological quality and adherence to standards of measurement. Implications for further research were given. The review wanted to answer the question whether HRV analysis provides a tool to measure the effect of manual medicine approaches on the ANS and it assessed the quality of measurement within the studies, as HRV analysis is dependent on multiple covariates that might tamper with the results of the trials.

The review was based on criteria of the Cochrane Collaboration (Chandler, Churchill, Higgins, Lasserson, & Tovey, 2013; Higgins & Green, 2011) and used aspects of the PRISMA (Preferred Reporting Item for Systematic Reviews and Meta-Analyses) Statement (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). To evaluate the methodological quality the "Downs and Black Checklist" was applied (Downs & Black, 1998).

3.3 Objectives

The aim was to systemically search for and assess studies that use heart rate variability analysis, either with time domain or frequency domain analysis methods, to demonstrate treatment effects of manual therapy, chiropractic care or osteopathic manipulative treatment on the autonomic nervous system. Studies could use a single or a sequence of techniques.

3.3.1 Criteria of Inclusion

Studies were included if they reported an empirical investigation in the field of manual medicine that was performed in humans and reported HRV (time domain or frequency domain metrics) and had at least 8 or more participants. The study population could be either healthy individuals or patients suffering from diseases. No age restriction was employed. Type of intervention could be either a single osteopathic or manipulative technique or a sequence of techniques. No restriction to a certain body part was employed. Unpublished dissertations were included.

3.3.2 Criteria of Exclusion

Not included in the review were case reports and case series, as the sample size is too small to make general assumptions. Studies with less than 8 participants were excluded. Furthermore, studies were excluded if they were only available as abstracts, because an investigation into quality of the assessed studies needs full-text information. Studies were excluded, if they were written in another language than German or English, due to lack of language capability of author.

3.3.3 Search Strategy

Between 2nd and 6th of October 2018 following databases were searched:

- AMED (Alternative Medicine Database)
- CINAHL (Cumulative Index to Nursing and Allied Health)
- COCHRANE Library
- EMBASE
- ICL (Index to Chiropractic Literature)
- OSTMED.DR (Osteopathic Medicine Digital Repository)
- OVID MEDLINE
- PubMed (US National Library of Medicine)
- PEDro (Physiotherapy Evidence Database)
- Scopus
- Web of Science ® Core Collection.

Furthermore, grey literature was included in terms of non-published undergraduate osteopathic research projects. They were identified by searching databases such as “Osteopathic Research Web”, which is hosted by the Osteopathic European Academic Network (OsEAN). As not all of the schools, who are members in this organisation, provide their studies on the mentioned database, their websites were searched respectively for relevant content. The data of the following two schools is available online:

- Escuela Universitaria de Osteopatía (Spain)
- Osteopathic Research Institute (Germany)

Search protocol also included databases of universities in New Zealand and Australia, because they also host Bachelor and Master degree programs:

- Royal Melbourne Institute of Technology RMIT (Australia)
- Victoria University (Australia)
- Unitec Institute of Technology (New Zealand)

3.3.3.1 Search Words

The following search terms were used:

The applied type of intervention:

- "manipulation", "manipulation, chiropractic", "manipulation, musculokeletal", "manipulation, orthopaedic", "manipulation, osteopathic", "manipulation, spinal", "manipulative medicine", "manual medicine", "manual therapy",
- "cranial osteopathy", "craniosacral osteopathy", "craniosacral therapy"
- "osteopathic", "osteopathic manipulative medicine", "osteopathic manipulative therapy", "osteopathic manipulative treatment"
- "chiropractic", "chiropractic adjustment", "spinal adjustment", "spinal manipulation", "spinal manipulative", "spinal mobilisation", "spinal mobilization".

in combination with:

- "heart rate variability", "RR variability", "power spectral analysis",
- "autonomic nervous system", "parasympathetic (nervous system)", "sympathetic (nervous system)",
- "vagal", "vagus nerve".

And for German publications respectively:

- "Osteopathie", "Osteopathische Medizin",
- "Manuelle Therapie", "Manualtherapie",
- "Chiropraktik",
- "craniosakrale Therapie",
- "Manipulation", "Mobilisation"

in combination with:

- "autonomes Nervensystem", "vegetatives Nervensystem", "Parasympathikus", parasympathisch", "Sympathikus", "sympathisch",
- "Herzfrequenzvariabilität", "Herzratenvariabilität", "Spektralanalyse".

The complete search strategies for each database can be found in the attachment (see Appendix A).

4 Results

4.1 Study Identification

PRISMA protocol (Liberati et al., 2009; Moher et al., 2009) was applied in the selection process of relevant publications. Removal of duplicates was performed with

Endnote™ X7.8. The systematic search identified a total of 16581 titles and abstracts. After excluding duplicates, 9172 abstracts were screened for inclusion. Obtaining full-text versions was not possible for 13 studies. 65 papers were screened in full-text, 20 studies did not match the defined inclusion criteria for following reasons, 9 papers were reviews, 2 case reports, 3 studies had less than 8 participants. Two studies (Cottingham, Porges, & Lyon, 1988; Cottingham, Porges, & Richmond, 1988) were excluded because they did not report changes in autonomic tone in time or frequency domain metrics, therefore no comparison could be made with the other studies. Two other studies (Beck, 2011; Zullow & Reisman, 1997) did not provide sufficient information suitable for assessment. 3 studies were excluded because they did not use either osteopathic, manual therapy or chiropractic techniques but massage techniques (Fazeli, Pourrahmat, Liu, Guan, & Collet, 2016; Hatayama et al., 2008; Wälchli et al., 2013). Leaving 23 studies and 8 unpublished research projects that were included in the review (see Figure 8).

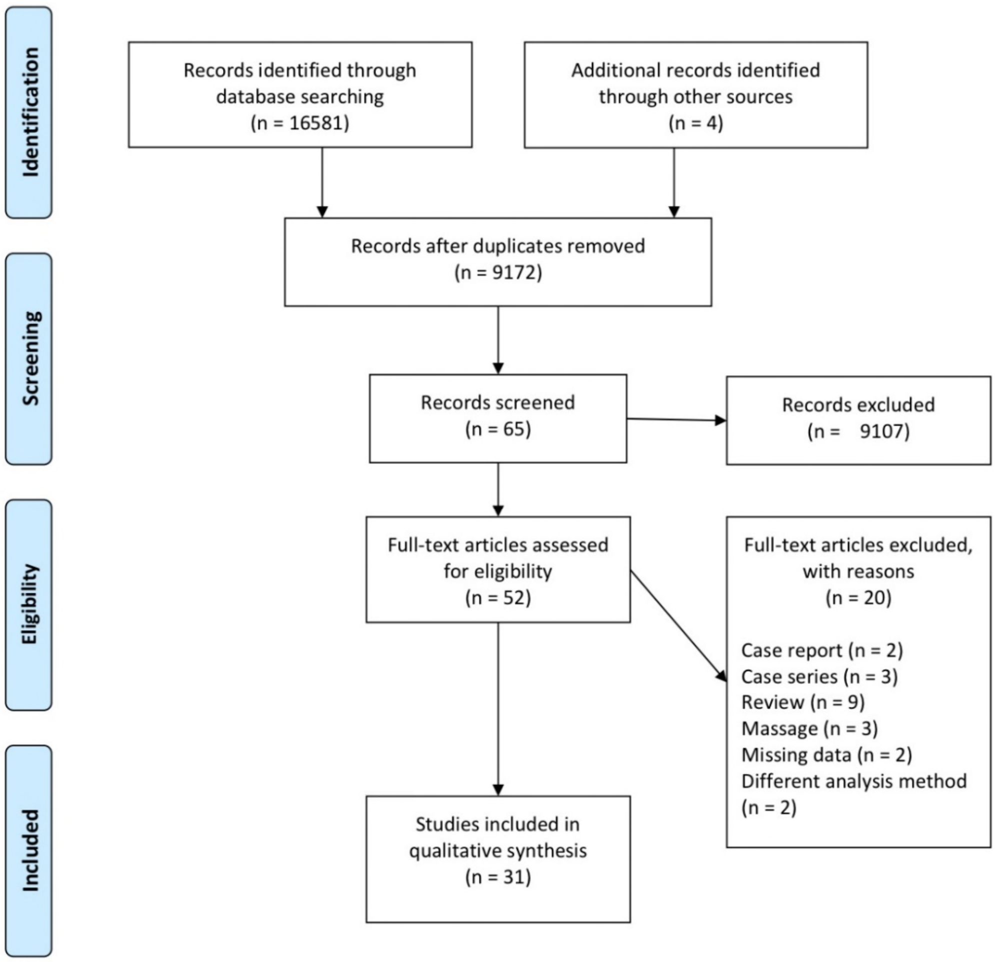

Figure 8. PRISMA Flowchart

Figure generated according to PRISMA protocol (Moher et al., 2009)

4.2 Data Extraction

The following meta-data from the included studies was extracted: year of publication, sample size, age and gender of the participants, type of condition (diagnosis or healthy individuals), type of intervention, and findings (see Table 1-2) and details of HRV recording (see Tables 3-4).

Table 1. Study Characteristics

Author	Study design	Population	Participants	Age range	Treatment	Recorded variables	Findings
Arroyo-Morales et al. (2008)	RCT	Healthy adults	62 (25 women, 37 men)	21.1±2.16 years	Single session of myofascial release for 40 min. vs. detuned ultrasound	SDNN, HRV index, LF, HF, LF/HF	Increase in HF (p<0.05)
Budgell & Hirano (2001)	Cross-over	Healthy adults	25 (5 women, 20 men)	21-40 (28.5±6) years	Single treatment with HVLA to C1, C2 vs. sham procedure	HR, LF/HF, LF, HF	Increase of LF (p = 0.0310). LF_{nu} (p=0.0061), LF/HF (p=0.0037), insignificant decrease of HF_{nu} (p0.6710)
Budgell & Polus (2006)	Cross-over	Healthy adults	28 (5 women, 23 men)	18-45 (29±7) years	Single treatment with HVLA to the thoracic spine vs. sham procedure	HR. LF/HF, LF, HF	Increase of LF (p=0.0098), LF_{nu} (p=0.0201), LF/HF (p=0.0030), decrease of HF (p=0.0043)
Castro-Sánchez et al. (2011)	RCT	Fibromyalgia	109 (105 women, 4 men)	38-64 (53.53±11.66) years	CST twice a week for 20 weeks CST without set protocol of techniques (1 hour) vs. sham (disconnected ultrasound (20 min.)	Pressure Pain, 24h SDNN, 24h RMSSD	No significant difference vs. baseline. Difference between intervention and placebo groups in SDNN (p < 0.043), RMSSD (p<0.046). Reduction in pain at 13 of the 18 tender points (p < 0.05)
Curi et al. (2018)	Controlled trial	Hypertensive vs. normotensive adults	30 men	50±6.67 years	Single treatment with CV4 (5 min.)	LF, HF, LF/HF	Decrease of LF in hypertensive group 10 min. post-treatment
Delaney et al. (2002)	pre-post	Healthy adults	30 (16 women, 14 men)	32.47±1.55 years	Single session with trigger point techniques applied to the head, neck and shoulder vs. control (rest)	SDNN, RMSSD, pNN, LF, HF	Increase in SDNN, RMSSD and pNN (p<0.01), Increase in HF (p=0.02)

Table 1. Study Characteristics (continued)

Author	Study design	Population	Partici-pants	Age range	Treatment	Recorded varia-bles	Findings
Fornari et al. (2017)	RCT	Healthy adults	20 men	20-30 years	Single treatment with 20 min. CST without protocol vs. sham treatment (light touch)	Salvia cortisol, HF, LF, LF/HF	Increase of AUCb values of HF_{nu} (r =2.08, p<0.056), decrease in LF/HF (r=-2.8, p<0.05)
Giles et al. (2013)	RCT	Healthy adults	19 (13 women, 6 men)	25±2 years	Single technique suboccipital decompression (15 min.) vs. sham (light touch) vs. time control (rest)	SDNN, HF, LF/HF	Increase of SDNN (p<0.001), HF (p=0.03), decrease of LF/HF (p=0.01)
Girsberger et al. (2014)	Cross-over	Patients with subjective dis-comfort	31 (16 women, 15 men)	19-60 years	Single treatment Upledger Ten-step-procedure (30 min) vs. time control (rest)	HR, SDNN, TP, LF/HF	Increase in SDNN (p<0.05), TP (p<0.01), no changes in LF/HF ratio
Henley et al. (2008)	Cross-over	Healthy adults	17 (8 women, 9 men)	19-50 years	Single session of cervical myo-fascial release in tilt position vs. sham treatment	HF, LF, LF/HF	Significantly less increase of LFnu and LF/HF in head up tilt position than sham or control (p<0.0001)
Hensel et al. (2013)	RCT	Pregnancy (30. week)	90 women	18-34 (23.13) years	Single session of 20-30 min. OMT to head, neck, abdomen, back, pelvis vs. detuned ultra-sound vs control (rest)	HF, LF	No difference in HRV between groups after treatment (p=0.36)
Milnes & Moran (2007)	Repeated measures	Healthy adults	10 (6 women, 4 men)	22-40 (29.8±6.3) years	Single CST technique (CV4) vs. sham treatment (light touch)	HF, LF	No significant difference between touch, CST and time control (p= 0.99, effect size d=0.20)

Table 1. Study Characteristics (continued)

Author	Study design	Population	Partici-pants	Age range	Treatment	Recorded varia-bles	Findings
Reis et al. (2014)	Controlled trial with immediate follow-up	Fibromyalgia vs. healthy adults	20 women	36-60 years	Single technique posteroante-rior glide mobilization between T1-T12	RMSSD, LF, HF, Poincaré plot, DFA	Decrease of RMSSD (p=0.003), HF_{nu} (p=0.036), SD1(p=0.003). Increase of LF_{nu} (p=0.016) DFAα1 (p=0.088), DFAα2 (p00.026)
Roy et al. (2009)	RCT	Healthy adults vs. adults with pain	53 (30 women, 23 men)	20-53 years	Single treatment with Activator or HVLA of L5 (lumbar roll) vs. sham treatment (positioning) vs. control (rest)	Mean RR, SDNN, NN50 count, pNN50. LF, HF, LF/HF	Decrease of LF in all groups except sham pain-free, LF/HF ratio decreased in treat-ment group (p= 0.46)
Ruffini et al. (2015)	Cross-over	Healthy adults	66 (32 women, 34 men)	26.7±8.4 years	Single session of BMT; BLT, CST (25 min.) vs. sham treat-ment (light touch)	HF, LF, LF/HF; DFAα1	Increase of HF_{nu} (p<0.001, effect size d=0.49), decrease in LF_{nu} (p<0.001), LF/HF (p<0.001), DFAα1 (p=0.09)
Scoppa et al. (2018)	RCT	Healthy adults	51 ? sex	24-40 years	10 min. CV4 or Dog technique	HF_{nu}. LF_{nu}, SDNN	Dog technique showed depression of the sympathetic component, CV4 depression of parasympathetic component.
Shafiq et al. (2014)	Controlled trial	Healthy adults vs patients with neck pain	20 (8 women, 12 men)	18-30 (22.0) years	One session of HVLA to the cervical spine (30 min.) vs. no intervention	LF, HF, LF/HF	Decrease of LF/HF (p=0.031)
Shi et al. (2011)	Multiple measurements	Healthy adults	21 (8 women, 13 men)	23-32 years	Single session of CV4 and augmentation technique vs. sham (light touch) each 4 min.	$Lf_{nu,}$, HF_{nu}	Increase of HF_{nu} for CV4 (p=0.035), Aug-mentation (p=0.032) and sham (p=0.035)

Table 1. Study Characteristics (continued)

Author	Study design	Population	Participants	Age range	Treatment	Recorded variables	Findings
Toro-Velasco et al. (2009)	Cross-over	Chronic tension type headache	11 (8 women, 3 men)	20-68 years	Single treatment of soft tissue techniques aimed at muscles of the head and neck (40 min.) vs. detuned ultrasound	PPT, index HRV, SDNN, RMSSD, LF, HF. mood state	Index HRV (p=0.04), no change in SDNN (p=0.8), RMSSD (p=0.3),LF (p=0.8), HF (p= 0,05)
Younes et al. (2017)	RCT	Acute back pain	22 men	?	Single treatment of HVLA, lumbar mobilization, muscular manipulations (45 min.) vs. sham treatment (positioning)	RMSSD, HF, LF/HF	Increase of RMSSD (p=0.003, effect size 0.52), LF/HF (p=0.429), HF (p=0.003, effect size = 0.33)
Watanabe & Polus (2007)	Pre-post	Healthy adults	11 (2 women, 9 men)	27±4.56 years	Single session of HVLA cervical region vs. sham treatment (positioning)	TP, LF, HF	no significant differences between HVLA and sham (p>0.05)
Win et al. (2015)	RCT cross-over	Healthy adults vs. patients with neck pain	20 (9 women, 11 men)	18-30 years	Single session of HVLA to the upper cervical spine (C1, C2) vs. HVLA to the lower cervical spine (C6. C7)	SDNN, HF_{nu}, LF/HF	Increase of SDNN and HF_{nu} (p=0.03) after upper and lower cervical HVLA in patients group (p=0.02)
Zhang et al. (2006)	Repeated measures, prospective	Patients with bodily pain (acute and chronic)	539 ? sex	46±15 years	Single treatment of HVLA or 4 session in 4 weeks	VAS, SDNN, RMSSD. LF, HF	After 1 session: Increase in SDNN (p<0.01), RMSSD (p<0.01), LF (p<0.05), HF (p<0.05) After 4 sessions: Increase in TP (p<0.05), LF (p<0.05), upper cervical HVLA and increase of LF/HF (p=0.02) after lower cervical HVLA in volunteer group, decrease of LF/HF (p>0.05)

Table 2. Study Characteristics (unpublished studies)

Author	Study design	Population	Participants	Age range	Treatment	Recorded variables	Findings
Beutinger (2011)	Prospective randomized, factorial 2*2	Low back pain	124 (83 w, 41 m)	53.18 ±10.53 years	10 session in 5 weeks of OMT with set protocol (45 min.) vs. PT	SDNN, RMSSD, PN50, 24 h HRV	Significant increase in all parameters, no significant change in 24 h measurement
Buschatzky (2014)	Controlled, single blinded	Healthy adults	45 (30 w, 15 m)	19-65 years	Single CST technique CV4 (20min.) vs. meditation vs. time control	RMSSD	Increase of RMSSD (p=0.0004)
Engel (2006)	Controlled, semi-randomized	Healthy adults	31	?	Single session of " synchronization with the slow rhythm" vs. sham (light touch) vs. time control	PCI, DAQ, LF/HF	No significant difference in LF/HF (p=0.677)
Fürpaß (2006)	Prospective, pre-post	Chronic disorders	12 (6 w, 6 m)	26-50 37,25±8.6 Years	4 session in 8 weeks with OMT (no protocol)	VAS, 24 h HRV	No significant difference after treatment
Hofer (2015)	Randomized parallel group	Healthy adults	32 w	20-56 years	Single session of myofascial release of the diaphragm	RMSSD	Significant increase of RMSSD (p<0.05)
Mayrhofer (2014)	Quantitative quasi-randomized	Healthy adults	56 (33 w. 23 m)	20-55 years	Single session of recoil to the sternum vs. light touch, vs. deep breathing, vs time control	SDNN	No significant difference between groups (p>0.05)

w= women, m= men

Table 2. Study Characteristics - unpublished studies (continued)

Author	Study design	Population	Participants	Age range	Treatment	Recorded Variables	Findings
Oliver et. al. (2003)	pre-post	Healthy adults	27 ? sex	18-65 years	1 session of suboccipital release	LF, HF	Increase of HF ($p = 0.026$)
White (2012)	Sham controlled pre-post	Healthy adults	18 (9w, 9m)	23.9±2.3 years	Single session of rib raising (10 min.) vs. sham procedure (light touch)	LF, HF; LF/HF	No significant difference between baseline measurement and between groups

w= women, m = men

Table 3. Characteristics of HRV Analysis (published studies)

Author	Type of recording	Sampling rate	Duration of measurement	Adaptation phase	Consideration of covariates	Monitoring of breathing	Circadian adaptation	Control for temperature	Control for artifacts
Arroyo-Morales et al. (2008)	ECG	128 Hz	5 min.	10 min.	-	-	✓	-	-
Budgell & Hirano (2001)	ECG	?	?	?	-	-	-	-	-
Budgell & Polus (2006)	?	?	?	?	-	-	-	-	-
Castro-Sánchez et al. (2011)	ECG	128 Hz	24 h.	-	✓	-	-	✓	-
Curi et al. (2018)	Polar RS800	1000 Hz	5 min.	5 min.	✓	-	-	-	✓
Delaney et al (2002)	ECG	?	5 min.	?	✓	-	✓	✓	✓
Fornari et al. (2017)	ECG	250 Hz	5 min.	15 min.	✓	✓	✓	✓	✓
Giles et al. (2003)	ECG	?	6 min.	20 min.	✓	✓	✓	?	-
Girsberger et al. (2014)	Universal Bodyware Mobile wellness cell phone (plethysmograph)	500 Hz	?	10 min.	✓	-	✓	✓	✓

Table 3. Characteristics of HRV Analysis (published studies) (continued)

Author	Type of recording	Sampling rate	Duration of Measurement	Adaptation phase	Consideration of covariates	Monitoring of breathing	Circadian Adaptation	Control for Temperature	Control for artifacts
Henley et al. (2008)	ECG	200 Hz	5 min.	10min.	✓	✓	✓	?	
Hensel et al. (2013)	ECG	?	5 min.	20 min.	-	-	-	-	-
Milnes & Moran (2007)	ECG	?	5 min.	10 min.	-	✓	-	✓	-
Reis et al. (2014)	Heart rate monitor (Polar S810i)	1000 Hz	?	-	✓	✓	-	✓	_
Ruffini et al. (2015)	HRV detector system Flexcomp	-	RR series of 300 beats	-	✓	✓	-	✓	-
Roy et al. (2009)	Heart rate monitor (Suunto T6)	?	?	8 min.	-	-	-	-	-
Scoppa et al. (2018)	SA3000P (photoplethysmograph)	?	5 min.	5 min.	-	-	-	-	-
Shafiq et al. (2014)	ECG	?	5 min.	10 min.	✓	-	-	-	-
Shi et al. (2011)	ECG	?	4 min.	15 min.	-	-	-	-	-
Toro-Velasco et al. (2009)	ECG	?	?	10 min.	-	-	✓	-	-

Table 3. Characteristics of HRV Analysis (published studies) (continued)

Author	Type of recording	Sampling rate	Duration of measurement	Adaptation phase	Consideration of covariates	Monitoring of breathing	Circadian adaptation	Control for temperature	Control for artifacts
Watanabe & Polus (2007)	ECG	?	10 min.	5 min.	✓	✓	-	✓	-
WIn et al. (2015)	ECG	400 Hz	-	5 min.	-	✓	-	✓	✓
Younes et al. (2017)	ECG	?	7 min.	-	✓	✓	✓	✓	✓
Zhang et al. (2006)	ECG	?	5 min.	5 min.	-	-	-	-	✓

Table 4. Characteristics of HRV Analysis (unpublished studies)

Author	Type of recording	Sampling rate	Duration of measurement	Adaptation phase	Consideration of covariates	Monitoring of breathing	Circadian adaptation	Control for temperature	Control for artifacts
Beutinger (2011)	HRV Scanner (ECG)	4000 Hz	1 min.	-	-	✓	-	-	✓
Buschatzky (2014)	IVNS MED chest strap (HF)	-	7-10 min. (520 beats)	5 min.	✓	-	-	-	-
Engel (2006)	Nerve Express (ECG)	-	2,25-3 min (192 beats)	-	-	-	-	-	✓
Fürpaß (2006)	HeartMan (ECG)	-	24h.	-	-	-	-	-	-
Hofer (2015)	Polar RS800CX (heart rate)	-	5 min.	✓	✓	-	✓	✓	✓
Mayrhofer (2014)	Emwave (plethysmograph)	-	2 min.	2 min.	-	-	-	-	-
Oliver et al. (2003)	BioCom (ECG)	-	?	-	✓	-	-	-	-
White (2012)	Polar s810i (heart rate)	1000 Hz	10 min.	2 min.	-	-	-	-	✓

4.3 Data Synthesis

19 studies were conducted with healthy volunteers, the others used patients with pain, either clearly defined as fibromyalgia (Castro-Sánchez et al., 2011; Reis et al., 2014), neck pain (Shafiq, McGregor, & Murphy, 2014; Win, Jorgensen, Chen, & Haneline, 2015), low back pain (Beutinger, 2011), acute back pain (Younes, Nowakowski, & Didier-Laurent, 2017), chronic tension type headache (Toro-Velasco, Arroyo-Morales, Fernández-de-las-Peñas, Cleland, & Barrero-Hernández, 2009), or diffuse categories such as “pain” (Roy, Boucher, & Comtois, 2009; Zhang, Dean, Nosco, Strathopulos, & Floros, 2006) or “subjective discomfort“ (Girsberger, Bänziger, Lingg, Lothaller, & Endler, 2014). One study used patients with “chronic disorders“ (Fürpaß, 2007). Pregnant women were assessed in one trial (Hensel, Pacchia, & Smith, 2013) and hypertensive patients were subjects in another (Curi, Maior Alves, & Silva, 2018).

The sample size ranged from 10 to 539 (median 27.5). Regarding the applied techniques, HVLA was applied to the cervical (Budgell & Hirano, 2001; Shafiq et al., 2014; Watanabe & Polus, 2007; Win et al., 2015), thoracic (Budgell & Polus, 2006) and lumbar spine (Roy et al., 2009; Younes et al., 2017), or generally without stating the localization (Zhang et al., 2006). One study used a mobilization technique for the thoracic spine (Reis et al., 2014), another one applied the “rib-rising technique“ (White, 2012). Craniosacral therapy (CST) was used in 9 trials, one applied a set protocol of the so-called “ten-step-procedure“ (Girsberger et al., 2014), five utilized the “CV4-technique“ (Buschatzky, 2014; Curi et al., 2018; Milnes & Moran, 2007; Scoppa et al., 2018; Shi et al., 2011), another one used the technique of “synchronizing with the slow rhythm“ (Engel, 2006), two simply stated that they applied CST (Castro-Sánchez et al., 2011; Fornari, Carnevali, & Sgoifo, 2017). Myofascial techniques to the atlantooccipital region (Giles, Hensel, Pacchia, & Smith, 2013; Oliver, Evans, & Dale Thompson, 2003), the neck (Henley, Ivins, Mills, Wen, & Benjamin, 2008; Toro-Velasco et al., 2009), the diaphragm (Hofer, 2015) were applied as single techniques. The sternum was treated with a recoil technique (Mayrhofer, 2014). Arroyo-Morales et al. (2008) applied myofascial release techniques after Upledger to multiple body regions but did not name them. One trial simple stated, that they applied OMT tailored to the individual findings of the patient (Fürpaß, 2007), one restricted OMT to craniosacral, BMT (balanced membranous tension) and BLT (balanced ligamentous tension) techniques (Ruffini et al., 2015). Two used a protocol, one named the utilized treatment methods and body regions (Hensel et al., 2013), the other one did not explain it at all (Beutinger,

2011). Three studies used trigger point techniques to the head and neck (Arroyo-Morales el al. 2008; Delaney et al., 2002; Toro-Velasco et al., 2009).
The majority of the studies (n=25) used frequency domain analysis to report their findings, 14 studies applied time domain analysis. Two studies reported their findings with a nonlinear method (DFA1α) (Reis et al., 2014; Ruffini et al., 2015).

4.4 Quality Assessment

Studies were assessed for quality by means of the Downs & Black checklist (Downs & Black, 1998) (see Table 5). "This scoring system is based on a checklist of 27 questions and has been found to be valid and reliable for critically evaluating experimental and non-experimental studies" (Jäkel & von Hauenschild, 2012, p.686). The questions assess reporting, internal and external validity. And according to the score the result can be categorized in "strong (score ≥ 21/27), moderate (score 14-20/27), limited (score 7-13/27) or poor (score <7/27)" (Jäkel & von Hauenschild, 2012, p. 686).
28 of the assessed studies have a moderate score, 3 a limited score (see Tables 6 and 7). This is due to the fact that only 8 studies are RCTs. 7 were cross-over trials. Thus, there is the possibility of bias as the patients were not blinded to the treatment they received. Some studies lack in reporting, they do not describe in detail the characteristics of the patients included in the study or fail to explain the treatment thoroughly. External validity was good in all studies.

Table 5. Downs & Black Checklist

	„Reporting		
1	Is the hypothesis / aim / objective of the study clearly described?	YES (1)	NO (0)
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	YES (1)	NO (0)
3	Are the characteristics of the patients included in the study clearly described?	YES (1)	NO (0)
4	Are the interventions of interest clearly described?	YES (1)	NO (0)
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	YES (1)	NO (0)
6	Are the main findings of the study clearly described?	YES (1)	NO (0)
7	Does the study provide estimates of the random variability in the data for the main outcomes?	YES (1)	NO (0)
8	Have all important adverse events that may be a consequence of the intervention been reported?	YES (1)	NO (0)
9	Have the characteristics of patients lost to follow up been described?	YES (1)	NO (0)
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	YES (1)	NO (0)

	External validity			
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	YES (1)	NO (0)	? (0)
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	YES (1)	NO (0)	? (0)
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	YES (1)	NO (0)	? (0)
	Internal validity – bias			
14	Was an attempt made to blind study subjects to the intervention they have received?	YES (1)	NO (0)	? (0)
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	YES (1)	NO (0)	? (0)
16	If any of the results of the study were based on „data dredging", was this made clear?	YES (1)	NO (0)	? (0)
17	In trials and cohort studies, do the analyses adjust for different length of follow-up of patients, or in case-control studies, is the time between the intervention and outcome the same for cases and controls?	YES (1)	NO (0)	? (0)
18	Were the statistical tests used to assess the main outcomes appropriate?	YES (1)	NO (0)	? (0)
19	Was the compliance with the intervention(s) reliable?	YES (1)	NO (0)	? (0)
20	Were the main outcome measure used accurate (valid and reliable)?	YES (1)	NO (0)	? (0)
	Internal validity – confounding (selection bias)			
21	Were the patients in different intervention groups (trials or cohort studies) or were cases and control (case-control) studies recruited from the same population?	YES (1)	NO (0)	? (0)
22	Were the patients in different intervention groups (trials or cohort studies) or were cases and control (case-control) studies recruited over the same time?	YES (1)	NO (0)	? (0)
23	Were the study subjects randomized to intervention groups?	YES (1)	NO (0)	? (0)
24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	YES (1)	NO (0)	? (0)
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	YES (1)	NO (0)	? (0)
26	Were losses of patients to follow-up taken into account?	YES (1)	NO (0)	? (0)
	Power			
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to change is less than 5%?" (Downs and Black, 1998, p. 362-384)	YES (1)	NO (0)	? (0)

Table 6. Quality Assessment with Downs & Black Checklist

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Sum
Arrroyo-Morales et al. (2008)	1	1	1	0	1	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	**16**
Budgell & Hirano (2001)	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	0	0	0	0	1	**17**
Budgell & Polus (2006)	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	0	0	0	0	1	**17**
Castro-Sánchez et al. (2011)	1	1	1	0	0	1	0	0	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	**16**
Curi et al. (2018)	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	**16**
Delaney et al. (2002)	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	**16**
Fornari et al. (2017)	1	1	1	0	1	1	0	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	**17**
Giles et al. (2013)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	**17**
Girsberger (2014)	1	1	0	1	0	1	0	0	0	0	0	0	1	0	0	0	1	1	1	0	1	1	0	0	0	0	1	**11**
Henley et al. (2008)	1	1	1	1	0	1	0	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	**17**
Hensel et al. (2013)	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	**16**
Milnes & Moran (2007)	1	1	1	1	1	1	0	0	0	1	1	1	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	**17**
Reis et al. (2014)	1	1	1	1	1	1	0	0	0	0	1	1	1	0	0	0	1	1	1	0	1	1	0	0	0	0	1	**15**

Questions 1-27 from Downs and Black Checklist (1998)

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Sum
Ruffini et al. (2015)	1	1	1	1	0	1	0	0	0	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	**16**
Roy et al. (2009)	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	**18**
Scoppa et al. (2018)	1	1	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	0	0	1	**11**
Shafiq et al. (2014)	1	1	0	1	0	1	0	0	0	0	1	1	1	0	0	0	0	1	1	1	0	1	0	0	0	0	1	**12**
Shi et al. (2011)	1	1	1	0	0	1	0	0	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0	0	1	**15**
Toro-Veslasco et al. (2009)	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	**17**
Watanabe & Polus (2007)	1	1	1	1	1	1	0	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	**18**
Win et al. (2015)	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1	0	1	0	0	0	0	1	**14**
Younes et al. (2017)	1	1	1	1	0	1	0	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	0	1	**18**
Zhang et al. (2006)	1	1	1	1	1	1	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	**15**

Questions 1-27 from Downs and Black Checklist (1998)

Table 7. Quality Assessment with Downs & Black Checklist (unpublished studies)

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Sum
Beutinger (2011)	1	1	1	0	1	1	0	0	1	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	**17**
Buschatzky (2014)	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	0	1	1	1	0	1	1	1	0	0	0	1	**16**
Engel (2006)	1	1	1	1	0	1	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	**17**
Fürpaß (2006)	1	1	1	0	1	1	0	0	0	0	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	**14**
Hofer (2015)	1	1	0	1	0	1	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1	1	1	0	0	0	1	**15**
Mayrhofer (2014)	1	1	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	1	**14**
Oliver et al. (2003)	1	1	0	1	0	1	0	0	0	0	1	1	1	0	0	0	0	0	1	0	1	1	0	0	0	0	1	**11**
White (2012)	1	1	0	1	0	1	0	0	0	0	1	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	1	**15**

Questions 1-27 from Downs & Balck (1988)

5 Discussion

5.1 Assessment of Technical Requirements and Quality of Measurement

HRV can be measured with ECG, mobile 24h-ECG, pulse watches with a chest strap or with finger photoplethysmography. The chest strap must fit properly and not interfere with breathing. Electrodes should be fixed on cleaned skin, which is free of any oily remains and hairs. Positioning of the electrodes according to normal standards of measurement is crucial for the quality of recording. Mispositioning increases the likelihood of artifacts (Sammito et al., 2014). Data retrieved with mobile chest strap devices show a high correlation to ECG-recordings at rest (r=1,000) and under physical stress (i.e. treadmill running) (r = 0,981) (Vanderlei, Silva, Pastre, Azevedo, & Godoy, 2008). Other studies reported similar high correlations, especially at rest (Sammito & Böckelmann, 2016). However, pulse watches provide no ECG trace, which can be used to better identify cardiac dysrhythmia, so there is likelihood for errors due to artifacts (Quintana et al., 2016).

Photoplethysmography is just an estimate of HRV and is only sufficiently accurate in healthy young subjects at rest. Photoplethysmography tends to overestimate HRV in variables associated with short-term variability (RMSSD, HF). Moderate stress tends to diminish agreement between pulse rate variability (PRV) and HRV, motion artifacts influence PRV to a high degree (Schäfer & Vagedes, 2013).

To obtain a maximum quality of measurement the following aspects should be considered (Sammito et al., 2014):

- The device used for recording beat-to-beat variations should use a sampling rate of at least 1000 Hz to guarantee accuracy.
- Conducting an ECG at rest to identify potential arrhythmias that influence HRV. If ectopic beats appear in more than 1% of the sampling, they tamper with HRV, because they feign a higher variability.
- Period of rest for 5-15 minutes before measurement.
- No smoking, eating, intake of caffeine or physical exercise at least half an hour before measurement.

Other authors propose even longer timescales, they recommend to “withhold caffeine and nicotine for at least 3-4 hours before testing, alcohol for 8 hours. If possible, sympathomimetic drugs should be stopped 24-48 hours before testing, and acetylcholine for 48 hours“ (Zygmunt & Stanczyk, 2010, p. 12). Directly before testing the patient should be positioned in a sitting or lying posture for at least 30 min.

before measurement in a quiet room with neutral temperature and humidity (Jaradeh & Prieto, 2003).
Movement can lead to artifacts, especially if one uses chest straps, these artifacts need to be controlled and removed with a special artifact detecting software.
Quintana et al. (2016) put forth a guideline for HRV measurement and interpretation, they propose that the device for HRV recording should be “validated against an ECG for accuracy, provide access to raw data, and offer technical details of correction methods“ (p. 4). Furthermore, they suggest an acclimatization period, this reduces any HRV changes due to posture, which may take time to adjust if the subject has just assumed supine or seated position.

This adjustment period was only applied in 19 studies that were included in the review at hand, the adjustment period was between 2 and 20 minutes (see Tables 3 and 4). 20 studies used ECG devices to record HRV. Most studies did not report the sampling rate of their recording device, thus making it difficult to draw assumptions on measurement accuracy. From the ten studies that did report the sampling rate, only 4 reported a sampling rate of 1000 Hz or higher. In 8 studies the duration of measurement was not in line with the recommendations of the Task Force (Malik et al., 1996), they reported lesser timeframes, 7 studies did not report the duration of measurement (see Tables 3 - 4).

5.2 Assessment of Covariates and Disturbing Factors in HRV Analysis

HRV is not only dependent on autonomic modulation, a number of intrinsic and extrinsic factors should be closely considered while preparing a study, because they can largely influence the results.

5.2.1 Respiration

HRV was originally discovered in relation to respiration - dependent variability. Respiratory sinus arrhythmia (RSA) is thought to reflect respiratory gated parasympathetic outflow to the heart via vagus nerve. During inhalation heart rate increases while during exhalation there is a decrease. The degree of coupling between heart rate and breathing is debated. RMSSD is not significant associated with respiration (Badra et al., 2001; Hill & Siebenbrock, 2009). For all other HRV parameters study results are inconclusive on the impact of respiration (Kanters, Hojgaard, Agner, & Holstein-Rathlou, 1997; Schaffer, Hensel, Weigand, Schüttler, & Jeleazcov, 2014). Schipke, Arnold, and Pelzer (1999) on the other hand found differences in HRV depending on the respiration rate: SDNN differed up to 33%, 37% in RMSSD and

75% in pNN50. LF differed up to 73% and HF up to 36% between different paced breathing rates.
Houtveen et al. (2002) suggested, that HRV indices adjusted for respiration parameters may in fact be less accurate indices of vagal influences than their unadjusted counterparts. Furthermore, Thayer et al. (2010) declared that recent data in respiratory physiology show that the heart beat might initiate the onset of inspiration. The causal direction might therefore flow from the cardiac change to respiration (Tzeng, Larsen, & Galletly, 2003). Monitoring respiration rate during HRV recording is still recommended during HRV recording (Allen et al., 2007; Billman, 2011) while the debate on the influence of respiration on HRV still continues.

Only 10 studies in this review monitored breathing during their trials (see Tables 3 - 4).

5.2.2 Age and Gender

HRV decreases with age (Umetani, Singer, McCraty, & Atkinson, 1998). The predictive value of HRV can be influenced in the elderly due to the normal decline making it hard to distinguish between disease and normal aging especially in subjects > 65 years old. HRV shows a significant negative correlation with aging, gender differences subsequently decrease. Beyond age 50, gender differences disappear for all time domain measures in 24-h. HRV recordings. SDNN index is most closely correlated with aging (Umetani et al., 1998).
The age - related decrease in HRV is greater for males than for females. Using SDNN, SDANN and SDNN index, HRV for male subjects begins to decrease significantly before age 30, shown in a study with 260 healthy subjects paired into age groups (10 to 99 years). Females in the same study exhibited a significant decrease only with respect to the comparison between the youngest (10 to 29 years) and oldest (70 to 99 years) groups for SDNNN and SDANN. Using SDNN index, HRV of females > 50 years old was significantly lower than that of young (10 to 29 years) subjects (Umetani et al., 1998). RSA, which is related to HF power, decreases linear with age from 20 to 80 years (Shannon, Carley, & Benson, 1987).
In a meta-analysis, females showed a significant lower mean RR interval and standard deviation of RR intervals (SDNN), the power spectral density is characterized by significantly less total power that contains significantly greater HF and less LF power thus influencing the LF/HF ratio (Thayer, Sollers, Friedman, & Koenig, 2016).

The gender differences also are significant regarding neuroimmunomodulation. An inverse association between HRV and C-reactive protein that was 4.4 times higher in females than in males was found (Thayer & Fischer, 2009).
In females, fluctuations in HRV also occur during menstrual cycle, a study found significant physiological differences between follicular and luteal phases by using power spectral analysis of HRV (Sato, Miyake, Akatsu, & Kumashiro, 1995). The luteal phase is associated with greater increase in the LF component and a greater decrease in the HF component, resulting in a higher LF/HF ratio. It is speculated that these changes result in high concentration levels of progesterone.

Most studies in this review made no effort to stratify for age or sex, 12 studies were conducted with young people who generally show higher HRV and adaptability than older participants (see Tables 1 - 2).
In the study by Roy et al. (2009) there was a significant difference in age regarding the intervention and the control group. The females in the treatment group were younger and thus per se demonstrated with higher variability.

5.2.3 Circadian Rhythm

HRV underlies a circadian rhythm, during nighttime HRV is higher than during the day (Boudreau, Dumont, Kin, Walker, & Boivin, 2011). One study (Bilan, Witczak, Palusiński, Myśliński, & Hanzlik, 2005) found peaks of hourly LF between 5 and 9 am and between 4 and 6 pm in healthy subjects. “The smallest LF was between 11 pm and 3 am. Hourly HF peaked between 11 pm and 5 am. The smallest HF was observed between midday and 2 pm“ (p. 239).
Of the 31 studies included in this review, 9 conducted their investigation during a standardized time frame, thus reducing circadian influence.
Hofer (2015) tried to demonstrate and effect of treatment adapted to the circadian rhythm. She assessed whether there is a difference if the patient was treated at the morning or in the afternoon. There is a slight tendency that the treatment showed more effect in the morning, but this might be due to the generally lesser sympathetic activity as mentioned before.
Moser (2006) argues, that after a treatment there might be an initial worsening in terms of ANS regulation. He prefers 24-h measurements. Regulation and signs of positive adaptation happen mainly during the night while sleeping. But the three studies (Beutinger, 2011; Castro-Sánchez et al., 2010; Fürpaß, 2006) that conducted long-term measurements failed to demonstrate significant treatment effect on HRV.

5.2.4 Sleep

Sleep deprivation is associated with an increase in LF and a decrease of HF. LF/HF ratio is compromised in subjects with higher working hours and lower sleeping periods (Ernst, 2014). None of the assessed studies mentioned effects of sleep quality on the study outcomes. In the three studies that conducted 24 - h. measurements, no remarks concerning sleep quality were made.

5.2.5 Medication

Several pharmacological substances influence the ANS, heart rate and HRV. Especially β- blocking agents, ACE- inhibitors, antiarrhythmica, and psychotropic drugs (Malik et al., 1996). As most studies were conducted with healthy volunteers this aspect plays a lesser role in this review.

5.2.6 Temperature

High temperature leads to higher sympathetic activity and reduced HRV (Ren et al., 2011). 11 of the reviewed studies considered the aspect of constant room temperature (see Tables 3 – 4).

5.2.7 Food Intake

Ingestion of meals does not lead to changes in HRV values, longer-lasting dietary restriction leads to an increase in HF and decrease in HF (Ernst, 2014). However, some of the reviewed studies took caution and instructed their study participants on food intake before the study. This is in line with the current recommendations (Sammito et al., 2014).

5.2.8 Intake of Nicotine, Alcohol and Caffeine

Caffeine increases HRV at rest, especially HF power, but leads to a higher decrease of HF power during and after progressive exercise, which suggests an exaggerated vagal withdrawal (Yeragani, Krishnan, Engels, & Gretebeck, 2005). Furthermore, caffeine as well as nicotine, increase the likelihood of ectopic beats (Quintana et al., 2016). Smoking reduces HRV, the effect is dose dependent (Cagirci et al., 2009). Even passive smoking reduces HRV (Felber Dietrich et al., 2007).

Intake of alcohol leads to short term reduction of HRV (Koskinen, Virolainen, & Kupari, 1994). Chronic substance abuse also reduces HRV (Monforte et al., 1995).

Intake of all these substances was considered by 15 studies in this review (see Tables 3 - 4).

5.2.9 Fitness Level

Endurance training leads to higher HRV (Aubert, Seps, & Beckers, 2003). The fitness level was not taken into account by any study except one (Arroyo-Morales et al., 2008). Curi et al. (2018) excluded participants that underwent intense exercises prior to the investigation.

5.2.10 Body Position

Body position can influence LF and HF components of HRV. In standing position the influence of sympathetic activity increases, expressed by increase of LF (Fagard, Pardaens, & Staessen, 2001).

Girsberger et al. (2014) assessed baseline measurement in a sitting posture and then switched to treatment in a horizontal posture, according to Watanabe, Reece, and Polus (2007) this might influence the results. They report that seated position is also associated with increase of LF and LF/HF ratio. Orthostasis plays a role in HRV measurement, an adaptation phase in the same posture is required to guarantee unaltered results. Hensel et al. (2013) conducted a tilt maneuver with their patients, but unfortunately, they had to change rooms for treatment and assessment. Therefore, the ambulatory phase between treatment and measurement might have tampered with the results.

Not all studies followed international guidelines, some of them recorded HRV in adequate time sequences (n= 12), and reported consideration of covariates (n= 15), monitoring of breathing (n= 10), and circadian adaptation (n= 13). Some studies used other devices than ECG or pulse watches to gain raw HR signals, these instruments are only partially validated against ECG signal recordings (see Tables 3-4). Thus, the quality of measurement is only moderate in the assessed studies.

5.3 Effect of Techniques

5.3.1 HVLA and Articular Techniques

At the level of the upper cervical spine HVLA resulted in different reactions of the ANS depending on the study. Budgell and Hirano (2001) found an increase of LF ($p = 0.0061$) and in LF/HF ratio ($p = 0.0031$) after manipulation of C1 and C2. While Watanabe and Polus (2007) reported no differences in HRV indices after application of HVLA, Shafiq et al. (2014) found a decrease of LF/HF ratio, this is in line with the results of Win et al. (2015) who also reported a decrease of LF/HF ratio ($p = 0.02$) after upper and lower cervical manipulation and an increase of HF ($p= 0.02$) in patients with neck pain. However, in the same study, the healthy volunteers presented with an increase of LF/HF ratio after lower cervical manipulation. The results with altered LF component and LF/HF ratio should be regarded with caution as they do not demonstrate changes in sympathovagal balance (Billman, 2011).

In the thoracic spine, Budgell and Polus (2006) found an increase of LF ($p = 0.0098$) after HVLA. Reis et al. (2014) also reported increase of LF_{nu} ($p = 0.016$) and decrease of HF_{nu} ($p = 0.036$) and RMSSD ($p = 0.003$) after posterior-anterior glide mobilization between T1-T12 in patients with fibromyalgia. White (2012) performed the "rib-raising technique" in a seated position and Mayrhofer (2014), who treated her patients with a recoil to the sternum, found no differences in HRV indices after the treatment in healthy adults. Stimulation of the thoracic spine and ribs seems to trigger a sympathetic response due to the location of the sympathetic trunc. However, this conclusion is questioned by Billman (2011) who does not attribute LF to the sympathetic system (see 2.2.2.2).

At the level of lumbar spine, Roy et al (2009) found a decrease of LF in adults with pain after HVLA. Scoppa et al. (2018) reported a depression of the sympathetic component after application of HVLA, but did not report exact values for LF and HF. On the other hand, Younes et al. (2017) found an increase of RMSSD ($p = 0.003$) and LF/HF ratio ($p = 0.429$) and HF ($p = 0.003$) after 45 min. of lumbar mobilization in patients with back pain.

Zhang et al. (2006) reported increase of variability after one session of HVLA in SDNN ($p < 0.01$) and RMSSD ($p < 0.01$) and controversly, they also found an increase both of LF and HF ($p< 0.05$) after one session and after 4 sessions of HVLA without giving information about the duration and site of treatment.

The results for the lumbar spine are conclusive and demonstrate an effect of HVLA on the parasympathetic nervous system. For the cervical and thoracic spine, the results are less clear as changes in HF were not reported robustly throughout the studies.

Previous reviews by Swensen (2011) and Bolton and Budgell (2012) concluded that spinal manipulation has an effect on ANS modulation, they also emphasize the need for rigorous adherence to measurement standards for HRV recordings. The author of the current review also suggests the reporting of covariates, more details of the recordings and the reporting of changes in HF and RMSSD rather than LF and LF/HF ratio.

5.3.2 Myofascial Release

For myofascial release techniques, most studies reported an increase of variability. Arroyo-Morales et al. (2008) found an increase of HF ($p < 0.05$) after a session of

40 min. For the suboccipital region, Giles et al. (2013) reported an increase of SDNN ($p < 0.001$), HF ($p = 0.03$) and a decrease of LF/HF ratio ($p = 0.01$) after suboccipital release. This is in line with the study from Oliver et al. (2003), who also found an increase of HF after application of the same technique. Henley et al. (2008) assessed the effect of a cervical myofascial release on baroreceptor activity in the tilt maneuver. They found less increase of LF_{nu} and LF/HF in head up tilt position in the treatment group ($p < 0.0001$) than in the sham or control group. Hofer (2015) could demonstrate a significant increase of RMSSD ($p < 0.05$) after a release to the diaphragm in healthy adults. Delaney et al. (2002) applied trigger point techniques to the head, neck and shoulder and reported an increase in SDNN, RMSSD ($p < 0.01$), and HF ($p = 0.02$) in healthy adults, while Toro Velasco et al. (2009) reported no effect of the same techniques in a population of patients suffering from fibromyalgia. Beutinger (2011) was unable to demonstrate a significant change in 24-h. HRV after treating patients with low back pain with myofascial techniques.

The evidence for the effect of myofascial techniques is conclusive and the results come from studies that presented with good quality and adherence to measurement standards. The conclusions of the author are in line with the review by Amaroso Borges et al. (2018) who also supported the reasoning that myofascial techniques have a modulating effect on ANS function.

5.3.3 Craniosacral Therapy

“CV4- technique“ was the subject of five trials, with controversial outcome. While Milnes and Moran (2007) found no significant difference between the application of the actual technique, sham (touch), and time control. Shi et al (2011) found an increase of HF_{nu} ($p = 0.035$) but also reported an increase in the sham group. On the other hand, Scoppa et al. (2018) reported a depression of the parasympathetic component. Curi et al. (2018) reported a decrease in LF, and Buschatzky (2014) reported an increase of RMSSD ($p = 0.0004$). The results of the last 3 trials provide reliable results and the studies are of a better quality than the other two.

Other single craniosacral techniques in the trials were the augmentation technique in the study conducted by Shi et al. (2011) that led to an increase of HF_{nu} ($p = 0.032$) but also in the sham group, and the technique of “synchronizing with the slow rhythm“ in the study conducted by Engel (2006), who found no significant difference between the application of the real technique and sham (light touch).

Castro-Sánchez et al. (2011) also reported no significant difference in 24- h. HRV after a treatment period of 20 weeks with 40 sessions of CST for 1 hour in patients with fibromyalgia. Fornari et al. (2017) found an increase of HF_{nu} ($p < 0.056$) and decrease of LF/HF ratio ($p < 0.05$) after 20 min. of CST in healthy adults. Girsberger et al. (2014) applied the “ten-steps-procedure“ and found an increase in SDNN ($p < 0.05$).

The conflicting results of the effect of craniosacral therapy were also mentioned by Jäkel and Hauenschild (2011, 2012). They concluded, that CST has no effect on HRV. However, the results of the trial by Fornari et al. (2017), which was not included in the previous review, is reliable and shows a positive effect of CST on ANS function.

5.3.4 General OMT

For longer sequences of treatment with the application of multiple techniques, Ruffini et al. (2015) reported an increase of HF_{nu} ($p < 0.001$), while Hensel et al. (2013) found no difference in the head up tilt manoeuver after OMT compared to detuned ultrasound. Fürpaß (2006) also could demonstrate no significant difference after 4 sessions of treatment.

For general OMT no previous review mentioned the conflicting results as the mentioned studies were incorporated in neither.

5.4 Effect on Specific Conditions

As 19 studies were conducted with healthy adults, no transfer for patients in general can be made. The body of evidence for specific conditions like low back pain, neck pain and fibromyagia is too sparse to draw general assumptions and the evidence is sometimes controversial. No generalization regarding treatment effect on certain age groups can be made. 10 studies assessed young patients, HRV is generally higher in younger adults (Nunan et al., 2010). Regarding the applied treatment approach, 4 studies failed to mention their applied techniques thus reducing the reproducibility of study results. Only 2 studies conducted follow-up measurements, therefore no long-term treatment effect could be assessed.

5.4.1 Fibromyalgia

A study by Castro-Sánchez et al. (2011) with patients suffering from fibromyalgia reported no changes in HRV. RMSSD was not significantly different after the treatment period of 20 week. However, regarding their second outcome measure pressure pain sensitivity, they reported significant reduction in pain over 13 of 18 assessed tender points ($p < 0.05$) at the first measurement directly after 20 weeks. There was a great age range in the study population (38-64 years). They only did two measurements of 24- h. HRV, one at the beginning and one at the end of these 20 weeks, short-term effects of each treatment therefore were not examined. The difference between treatment and control group indicates a treatment effect on

HRV. SDNN ($p < 0.043$) and RMSSD ($p < 0.046$) differed between groups. Reis et al. (2014) assessed the effect of a single mobilization technique to the thoracic spine in patients with fibromyalgia vs. healthy control. They found a decrease in RMSSD, HF_{nu} and SD1, indicating a sympathetic response to the treatment. So the results are conflicting. Castro-Sánchez et al. (2011) assessed only patients while Reis et al. (2014) compared healthy subjects with patients, therefore the results of Castro-Sánchez et al. (2011) are more significant.

5.4.2 Neck Pain

Shafiq et al. (2014) and Win et al. (2015) assessed the treatment effect in patients with neck pain, but the results differ. While Shafiq et al. (2014) found a decrease of LF/HF ratio ($p = 0.031$), Win et al. (2015) found a decrease of LF/HF ratio ($p = 0.02$) only in the patient group, the volunteers presented with an increase of LF/HF ratio ($p = 0.02$) after lower cervical HVLA. Maybe patients respond differently than healthy subjects.

5.4.3 Back Pain

Younes et al. (2017) found an increase of RMSSD and HF after HVLA to the lumbar spine. This is in line with the findings of Roy et al. (2009) who also reported a decrease of LF.

The results for back pain are therefore conclusive, stimulation of the lumbar spine triggers a parasympathetic response.

5.5 Quality of the Studies

Most studies lack in terms of size of study population and quality of measurement. The quality of the studies assessed with the Downs & Black Checklist is only moderate. The Downs and Black Checklist does not totally reflect the quality of the studies as some questions could only be scored for RCT’s and it is therefore not the ideal instrument to assess the quality of so many different study designs. Higgins and Green (2011) point out, that scores do not reflect the quality of trials but rather the single items should be evaluated. This was the reason for using this checklist, as the multiple items clearly reflect the quality of the study, especially items like reporting and usage of validated outcome measures were important for the author. As described in the introduction, the review wants to provide a broad picture of the available research and therefore included studies of all kind.

5.6 Limitations

5.6.1 Publication Bias

Although the search, which included all major databases, was performed thoroughly, this review still suffers from a slight publication bias, as 13 studies were only available as abstracts and therefore could not been evaluated properly. A significant number of these studies presented with inconclusive results, which may lead to a potential bias, as mainly positive results were published in official journals. Furthermore, not all osteopathic study programmes publish the undergraduate work of their students online, so there might exist an even larger body of evidence in this field.

5.6.2 Internal Limitations

Normally, a systematic review is the joined effort of a couple of peers. At least two reviewers should assess the studies to limit a potential bias in the selection and evaluation process (Higgins & Green, 2012). To minimize this effect, the complete search strategy of this work is available as supplement (see Appendix A), so the search can be reproduced by anyone.

Generally, one favours articles which have undergone a peer-review process and are published in renowned journals with a high impact factor. As the author conducted all phases of the review herself, she was aware where the papers were published, so the aforementioned effect cannot be fully denied.

Current guidelines for reviews (Higgins & Green, 2011) encourage authors to include papers in all languages. However, in this work only German and English studies are incorporated, so a slight language bias remains.

Due to limited access options to certain databases (i.e. AMED, SCOPUS), who are only available onsite of Danube University campus, the review at hand may already be outdated since completing the search for this project in October 2018.

In hindsight, the use of the Downs and Black Checklist could be questioned, as only RCTs can achieve top scores. However, if one looks at the questions separately, useful information on reporting and study quality can be drawn even for non-RCT trials. If only RCTs had been included in the review, the picture of the current research would have been incomplete and the recommendations and conclusions drawn would not be so useful for further research projects.

6 Conclusion

6.1 Summary

At this point, the available body of research is still sparse, further studies with larger study populations are recommended and rigorous adherence to and reporting of standards of measurements are required.

There is a tendency that spinal manipulation applied to the cervical and lumbar spine increases HRV and HF in particular, and at the thoracic spine increases LF. Myofascial techniques also increase HF. For craniosacral therapy and general OMT the results are conflicting, but there is a tendency that they both increase the variability, especially RMSSD, SDNN and HF, thus having an impact on the ANS. Therefore, the research question whether manual medicine approaches have an effect on the ANS can only partially be answered. HRV is a valid tool to assess ANS changes but requires adherence to measurement standards and consideration of covariates.

6.2 Implications for Research and Practice

6.2.1 Adherence to Standards of Recording and Data Analysis

Future research projects using HRV as surrogate marker for ANS function should adhere to established guidelines for measurement and data processing. This enables the comparability of studies, and is crucial for reviews, who compare the effect sizes of different treatment approaches. The utilization of approved measurement devices and validated software should be self-evident, as they allow for minimization of artifacts in recording. External and internal disturbing factors and covariates, as mentioned in the previous discussion, should always be considered.

Outside rigorous study protocols, commercial HRV-recording devices, like pulse watches, that provide valid data, low-cost HRV-software, measurement devices and smartphone applications, can be incorporated for self-monitoring, bio-feedback therapy and evaluation of training effects.

Interpretation of LF/HF ratio should be done with caution, it does not reflect sympathovagal balance (Billman, 2013). Only HF and time domain measures like SDNN and RMSSD should be assessed.

6.2.2 Application of Multiple Assessments

The author dissuades the usage of HRV as single outcome measurement. For short time evaluations of changes in ANS activity, other physiological markers like salivary cortisol, skin conductance and peripheral arterial resistance are also feasible.

Salivary cortisol is routinely used as biomarker of psychological stress and related mental or physical diseases (Hellhammer, Wüst, & Kudielka, 2009) and was already successfully used together with HRV analysis by Fornari et al. (2017) in their pilot study.

Long-term (24-hour) recordings are better suited to reflect the treatment effect on the ANS, especially on parasympathetic activity. Treatment may show its effect not immediately after application, but during the next resting period. Sleep quality, therefore, is a suitable index for treatment response as Cutler et al. (2005) demonstrated. Moser's chronotropic image could be used to assess the sleep quality with regard to the ANS function (Moser et al., 2008).

Cortisol and TNF -alpha as biomarkers for inflammation and stress response can be used as additional samples to demonstrate the recovery after stress like demonstrated by Weber et al. (2010).

6.2.3 Healthy Volunteers vs. Patients

Conducting studies with healthy volunteers is easier than recruiting patients, but the response to the treatment might differ, because the patients already present with lower HRV values.

Furthermore, research should focus on chronic pain, functional somatic disorders (e.g. fibromyalgia, irritable bowel syndrome) and psychiatric disorders (chronic fatigue syndrome, depression). This is also relevant for stakeholders in the Public Healthcare System who are interested in reducing the costs that these diseases cause.

6.2.4 Utilization of Semi-Standardized Study Protocols

Osteopathic studies should not focus on evaluating the effect of single techniques. This does not reflect osteopathic practice, which normally incorporates a series of techniques. Semi-standardized treatment protocols with a sequence of techniques addressing potential key regions and structures are therefore more authentic. Clearly set protocols also enhance the reproducibility of trials.

There are a few studies that already implemented such a protocol, they describe certain sequences that could be varied at the discretion of the practitioners based on their clinical findings in the individual patient while still addressing relevant key areas (Fryer, Alvizatos, & Lamaro, 2005; Noll, Degenhardt, Fossum, & Hensel, 2008). This adaptation is in line with the patient-centered approach of OMM, which is always adapted to the individual findings, signs and symptoms of each patient. Although the "ten-step-procedure" that was applied by Girsberger et al. (2014)

demonstrated an effect on the ANS, other treatment protocols that address all possible impediments or sites of entrapment in the course of the vagal nerve, or include more cranial techniques than just CV4, warrant further investigation.

6.2.5 Comparison of Osteopathic Techniques with other CAM Methods

In the field of massage therapy, a number of interesting studies exist, that were not included in the review at hand. Massage has an effect on ANS activity and stress response (Lindgren et al., 2010). Especially the application of soft tissue techniques (Fazeli et al., 2016; Hatayama et al., 2008) at the head and neck, seem to have an effect on vagal and trigeminal afferents and by proxy on HRV and on psychological parameters, such as anxiety.

Acupuncture can influence ANS activity and induce changes in HRV parameters (Chung et al., 2014). Another method, which activates the vagal nerve and modulates HRV is t-VNS (vagal nerve stimulation), a new way to influence pain by electrical stimulation of the auricular branch of the vagal nerve (Clancy et al., 2014). This method with a costly device is currently investigated for the treatment of migraine (Straube, Ellrich, Eren, Blum, & Ruscheweyh, 2015).

All of the above - mentioned therapeutic methods could be incorporated in a study as comparison to OMM.

6.2.6 Practice-Based Research Networks

A major point of critique about trials in the osteopathic field is the sample size and the small study populations. This is often found in undergraduate work due to lack of financial funding and time restraints.

Multi-site trials might be a way to generate larger study groups. Practice-based research networks (PBRN) are a way to organize such endeavors. The Cochrane Institute offers a guideline on this topic (Voigt-Radloff et al., 2016) and there already exists an collaboration for osteopaths who want to conduct research in the field of their practice, out of university settings ("DO-touch.NET," 2018).

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Tables

Figures

Abbreviations

ANS	autonomic nervous system
BMT	balanced membranous tension technique
BLT	balance ligamentous tension technique
CST	craniosacral therapy
DAQ	Dimensions of Attention Questionnaire
DFAα	detrended fluctuation analysis
HF	high frequency band of HRV
HPA	hypothalamic-pituitary-adrenal (axis)
HR	heart rate
HRV	heart rate variability
HVLA	high velocity low amplitude spinal manipulation technique
IBI	interbeat interval
LF	low frequency band of HRV
MeSH	Medical Subject Heading
NA	Nucleus ambiguous
NN50	Number of N–N intervals differing by > 50 ms from the preceding interval
NTS	Nucleus tractus solitarius
OMT	osteopathic manipulative treatment
OMM	osteopathic manipulative medicine
PCI	Phenomenology of Consciousness Inventory
pNN50	percentage of adjacent cycles that are >50 ms apart
PNS	parasympathetic nervous system
PPT	pressure pain threshold
PT	physiotherapy
RCT	randomized controlled trial
RMSSD	root mean square successive differences in milliseconds
RR	mean value of all normal-to-normal interbeat (N–N) intervals
RSA	respiratory sinus arrhythmia
SDANN	standard deviation of the average N–N intervals for each 5-min. period over 24 h.
SDNN	standard deviation of all N–N intervals
SDNNindex	average of the standard deviations of N–N intervals for each 5-min period
SNS	sympathetic nervous system
TP	total power of RR-intervall variability

VAS	visual analog scale for pain rating

Appendix A: Supplementary Data

AMED Search on 2.10.2018

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Suche **Zeitschriften** **Meine Multimedia-Ressourcen** **Mein Arbeitsbereich**

▼ Suchverlauf (12) Gespeicherte Suchen

# ▲	Suchen	Ergebnisse	Typ	Aktionen	Annotationen
1	((heart rate variability or HRV or RR-variability or spectral analysis) and (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)).af.	17	Erweitert	Ergebnisse | Mehr anzeigen	
2	((heart rate variability or HRV or RR-variability or spectral analysis) and (manipulative medicine or manual medicine or manual therapy)).af.	3	Erweitert	Ergebnisse | Mehr anzeigen	
3	((heart rate variability or HRV or RR-variability or spectral analysis) and (cranial osteopathy or craniosacral osteopathy or craniosacral therapy)).af.	1	Erweitert	Ergebnisse | Mehr anzeigen	
4	((heart rate variability or HRV or RR-variability or spectral analysis) and (osteopathic or osteopathic manipulative medicine or osteopathic manipulative therapy or osteopathic manipulative treatment)).af.	3	Erweitert	Ergebnisse | Mehr anzeigen	
5	((heart rate variability or HRV or RR-variability or spectral analysis) and (chiropractic or chiropractic adjustment or spinal adjustment or spinal manipulation or spinal manipulative or spinal mobilisation or spinal mobilization)).af.	13	Erweitert	Ergebnisse | Mehr anzeigen	
6	((heart rate variability or HRV or RR-variability or spectral analysis) and (connective tissue therapy or connective tissue treatment or massage or myofascial or myofascial release therapy or therapy, soft tissue or soft tissue therapy or soft tissue treatment)).af.	16	Erweitert	Ergebnisse | Mehr anzeigen	
7	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)).af.	53	Erweitert	Ergebnisse | Mehr anzeigen	
8	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (manipulative medicine or manual medicine or manual therapy)).af.	20	Erweitert	Ergebnisse | Mehr anzeigen	
9	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (cranial osteopathy or craniosacral osteopathy or craniosacral therapy)).af.	6	Erweitert	Ergebnisse | Mehr anzeigen	
10	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (osteopathic or osteopathic manipulative medicine or osteopathic manipulative therapy or osteopathic manipulative treatment)).af.	13	Erweitert	Ergebnisse | Mehr anzeigen	
11	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (chiropractic or chiropractic adjustment or spinal adjustment or spinal manipulative or spinal mobilisation or spinal mobilization)).af.	59	Erweitert	Ergebnisse | Mehr anzeigen	
12	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (connective tissue therapy or connective tissue treatment or massage or myofascial or myofascial release therapy or therapy, soft tissue or soft tissue therapy or soft tissue treatment)).af.	45	Erweitert	Ergebnisse | Mehr anzeigen	

die letzten Suchen

CINAHL search on 2.10.2018

EBSCOhost

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#	Query	Limiters/Expanders	Last Run Via	Results
S15	(autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) AND (chiropractic or chiropractic adjustment or spinal adjustment or spinal manipulation or spinal manipulative or spinal mobilisation or spinal mobilization)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	110
S14	(autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) AND (osteopathic OR osteopathic manipulative medicine or osteopathic manipulative therapy or osteopathic manipulative treatment)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	28
S13	(autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) AND (cranial osteopathy Or craniosacral osteopathy or craniosacral therapy)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	16
S12	(autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) AND (manipulative medicine Or manual medicine or manual therapy)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	82
S11	(autonomic nervous system or sympathetic	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases	156

	spinal mobilisation or spinal mobilization)			
S7	(heart rate variability or hrv or rr-variability or spectral analysis) AND (osteopathic Or osteopathic manipulative medicine Or osteopathic manipulative therapy or osteopathic manipulative treatment)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8
S6	(heart rate variability or hrv or rr-variability or spectral analysis) AND (cranial osteopathy or craniosacral osteopathy or craniosacral therapy)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1
S5	(heart rate variability or hrv or rr-variability or spectral analysis) AND (manipulative medicine or manual medicine or manual therapy)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	26
S4	(heart rate variability or hrv or rr-variability or spectral analysis) AND (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	54
S3	(heart rate variability or hrv or rr-variability or spectral analysis) AND (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0

	manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)			
S2	MM "Low Back Pain"	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	10,283
S1	(heart rate variability or hrv or rr-variability or spectral analysis) AND (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	54

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Cochrane Library

Advanced Search

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No.	Search	Results
#1	(heart rate variability AND manipulation OR manipulation, chiropractic OR manipulation, musculoskeletal OR manipulation, orthopedic OR manipulation, osteopathic OR manipulation, spinal):ti,ab,kw (Word variations have been searched)	2248
#2	heart rate variability AND "manipulative Medicine" OR "manual Medicine" OR "manual therapy"	1312
#3	"heart rate variability" AND "cranial osteopathy" OR "craniosacral osteopathy" OR "craniosacral therapy"	36
#4	"heart rate variability" AND "osteopathic" OR "osteopathic manipulative"	222
#5	"heart rate variability" AND "chiropractic" OR "chiropractic Adjustment" OR "spinal Adjustment" OR "spinal Manipulation" OR "spinal manipulative" OR " spinal Mobilisation" OR "spinal mobilization"	713
#6	"heart rate variability" AND "connective tissue therapy" OR "massage" OR "myofascial" OR "therapy, soft tissue"	5067
#7	Manually type a search term here or click on the S (Search Wizard) or MeSH button to compose one	N/A

Clear all

Highlight orphan lines

EMBASE search on 2.10.2018

Embase

Embase Session Results

No.	Query	Results
#17	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('myofascial release'/exp OR 'myofascial release')	4
#16	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('massage'/exp OR 'massage')	361
#15	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('craniosacral therapy'/exp OR 'craniosacral therapy')	8
#14	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('chiropractic'/exp OR 'chiropractic')	79
#13	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('orthopedic manipulation'/exp OR 'orthopedic manipulation')	13
#12	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('osteopathic manipulation'/exp OR 'osteopathic manipulation')	8
#11	('autonomic nervous system'/exp OR 'autonomic nervous system') AND ('osteopathic medicine'/exp OR 'osteopathic medicine')	224
#10	'autonomic nervous system'/mj AND 'manipulative medicine'/mj	16
#9	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND ('myofascial release'/exp OR 'myofascial release')	3
#8	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND ('massage'/exp OR massage)	57
#7	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND ('craniosacral therapy'/exp OR 'craniosacral therapy')	0
#6	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND ('chiropractic'/exp OR chiropractic)	30
#5	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND orthopedic AND ('manipulation'/exp OR manipulation)	4
#4	(heart AND rate AND variability OR hrv OR 'rr variability' OR spectral) AND analysis AND 'osteopathic manipulation'	1
#3	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND osteopathic AND ('medicine'/exp OR medicine)	32
#2	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND osteopathic AND ('medicine'/exp OR medicine)	32
#1	(('heart'/exp OR heart) AND rate AND ('variability'/exp OR variability) OR hrv OR 'rr variability' OR spectral) AND ('analysis'/exp OR analysis) AND manipulative AND ('medicine'/exp OR medicine)	21

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▼ Suchverlauf (12) — Gespeicherte Suchen

# ▲	Suchen	Ergebnisse	Typ	Aktionen	Annotationen
1	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (connective tissue therapy or connective tissue treatment or massage or myofascial release therapy or therapy, soft tissue or soft tissue therapy or soft tissue treatment)).af.	298	Erweitert	Ergebnisse | Mehr anzeigen	
2	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (chiropractic or chiropractic adjustment or spinal adjustment or spinal manipulation or spinal manipulative or spinal mobilisation or spinal mobilization)).af.	77	Erweitert	Ergebnisse | Mehr anzeigen	
3	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (osteopathic or osteopathic manipulative medicine or osteopathic manipulative therapy or osteopathic manipulative treatment)).af.	161	Erweitert	Ergebnisse | Mehr anzeigen	
4	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (cranial osteopathy or craniosacral osteopathy or craniosacral therapy)).af.	4	Erweitert	Ergebnisse | Mehr anzeigen	
5	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (manipulative medicine or manual medicine or manual therapy)).af.	57	Erweitert	Ergebnisse | Mehr anzeigen	
6	((autonomic nervous system or sympathetic or parasympathetic or vagal or vagus) and (manipulation or manipulation, chiropractic or manipulation musculoskeletal or manipulation orthopedic or manipulation, osteopathic or manipulation, spinal)).af.	758	Erweitert	Ergebnisse | Mehr anzeigen	
7	((heart rate variability or hrv or rr-variability or spectral analysis) and (manipulation or manipulation, chiropractic or manipulation, musculoskeletal or manipulation, orthopedic or manipulation, osteopathic or manipulation, spinal)).af.	155	Erweitert	Ergebnisse | Mehr anzeigen	
8	((heart rate variability or hrv or rr-variability or spectral analysis) and (manipulative medicine or manual medicine or manual therapy)).af.	23	Erweitert	Ergebnisse | Mehr anzeigen	
9	((heart rate variability or hrv or rr-variability or spectral analysis) and (cranial osteopathy or craniosacral osteopathy or craniosacral therapy)).af.	2	Erweitert	Ergebnisse | Mehr anzeigen	
10	((heart rate variability or hrv or rr-variability or spectral analysis) and (osteopathic or osteopathic manipulative medicine or osteopathic manipulative therapy or osteopathic manipulative treatment)).af.	17	Erweitert	Ergebnisse | Mehr anzeigen	
11	((heart rate variability or hrv or rr-variability or spectral analysis) and (chiropractic or chiropractic adjustment or spinal adjustment or spinal manipulation or spinal manipulative or spinal mobilisation or spinal mobilization)).af.	29	Erweitert	Ergebnisse | Mehr anzeigen	
12	((heart rate variability or hrv or rr-variability or spectral analysis) and (connective tissue therapy or connective tissue treatment or massage or myofascial release therapy or therapy, soft tissue or soft tissue therapy or soft tissue treatment)).af.	81	Erweitert	Ergebnisse | Mehr anzeigen	

die letzen Suchen

PubMed Search on 2.10.2018

History

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Search	Add to builder	Query	Items found	Time
#50	Add	Search **(autonomic nervous system) AND therapy, soft tissue**	145	09:46:46
#48	Add	Search **(autonomic nervous system) AND myofascial**	59	09:45:56
#46	Add	Search **(autonomic nervous system) AND massage**	212	09:45:14
#45	Add	Search **(autonomic nervous system) AND "cranial osteopathy" OR "craniosacral therapy" OR "craniosacral osteopathy"**	63	09:44:08
#44	Add	Search **(autonomic nervous system) AND "manual medicine"**	3	09:43:02
#42	Add	Search **(autonomic nervous system) AND "manual therapy"**	32	09:42:10
#41	Add	Search **(autonomic nervous system) AND manual therapy**	263	09:41:33
#39	Add	Search **(autonomic nervous system) AND manipulative medicine**	18	09:41:24
#38	Add	Search **(autonommic nervous system) AND manipulative medicine**	86	09:40:46
#34	Add	Search **(autonomic nervous system) AND manipulation, spinal**	93	09:39:45
#32	Add	Search **(autonomic nervous system) AND manipulation, osteopathic**	20	09:38:38
#30	Add	Search **(autonomic nervous system) AND manipulation, orthopedic**	19	09:38:01
#28	Add	Search **(autonomic nervous system) AND manipulation, musculoskeletal**	12	09:37:30
#26	Add	Search **(autonomic nervous system) AND manipulation, chiropractic**	22	09:36:40
#24	Add	Search **(heart rate variability) AND therapy, soft tissue**	49	09:34:44
#22	Add	Search **(heart rate variability) AND myofascial**	16	09:33:56
#19	Add	Search **(heart rate variability) AND massage**	65	09:32:59
#17	Add	Search **(heart rate variability) AND chiropractic**	17	09:31:42

Search	Add to builder	Query	Items found	Time
#14	Add	Search **(heart rate variability) AND "cranial osteopathy" OR "craniosacral osteopathy" OR "craniosacral therapy"**	63	09:29:04
#12	Add	Search **(heart rate variability) AND manual therapy**	105	09:27:48
#10	Add	Search **(heart rate variability) AND manual medicine**	34	09:27:05
#8	Add	Search **(heart rate variability) AND manipulative medicine**	8	09:26:21
#5	Add	Search **(heart rate variability) AND manipulation, spinal**	15	09:24:53
#4	Add	Search **(heart rate variability) AND manipulation, osteopathic**	5	09:23:59
#3	Add	Search **(heart rate variability) AND manipulation, orthopedic**	1	09:23:31
#2	Add	Search **(heart rate variability) AND manipulation, musculoskeletal**	2	09:22:55
#1	Add	Search **(heart rate variability) AND manipulation, chiropractic**	7	09:22:33

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6	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "connective tissue therapy" OR "connective tissue treatment" OR "massage" OR "myofascial" OR "myofascial release therapy" OR "therapy, soft tissue" OR "soft tissue therapy")	123 document results
5	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "chiropractic" OR "chiropractic adjustment" OR "spinal adjustment" OR "spinal manipulation" OR "spinal manipulative" OR "spinal mobilisation" OR "spinal mobilization")	27 document results
4	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "osteopathic" OR "osteopathic manipulative")	16 document results
3	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "cranial osteopathy" OR "craniosacral osteopathy" OR "craniosacral therapy")	2 document results
2	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "manipulative medicine" OR "manual medicine" OR "manual therapy")	31 document results
1	TITLE-ABS-KEY ("heart rate variability" OR hrv OR " RR-variability" OR "Spectral analysis" AND "manipulation" OR "manipulation, chiropractic" OR "manipulation, musculoskeletal" OR "manipulation, orthopedic" OR "manipulation, osteopathic" OR "manipulation, spinal")	373 document results

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Set	Results		Edit Sets
# 13	18	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (osteopathic OR osteopathic manipulative) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 12	4	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (cranial osteopathy OR craniosacral osteopathy OR craniosacral therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 11	213	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (chiropractic OR chiropractic adjustment OR spinal adjustment OR spinal manipulation OR spinal manipulative OR spinal mobilisation OR spinal mobilization) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 10	4	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (cranial osteopathy OR craniosacral osteopathy OR craniosacral therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 9	77	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (manipulative medicine OR manual medicine OR manual therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 8	134	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (manipulation, chiropractic OR manipulation, muskuloskeletal OR manipulation, orthopedic OR manipulation, osteopathic OR manipulation, spinal) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 7	402	**TOPIC:** (autonomic nervous system OR sympathetic OR parasympathetic OR vagal OR vagus) *AND* **TOPIC:** (connective tissue therapy OR connective tissue treatment OR massage OR myofascial OR myofascial release therapy OR therapy, soft tissue OR soft tissue therapy OR soft tissue treatment) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 6	92	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (connective tissue therapy OR connective tissue treatment OR massage OR myofascial OR myofascial release therapy OR therapy, soft tissue OR soft tissue therapy OR soft tissue treatment) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 5	26	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (chiropractic OR chiropractic adjustment OR spinal adjustment OR spinal manipulation Or spinal manipulative OR spinal mobilisation OR spinal mobilization) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 4	14	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (osteopathic OR osteopathic manipulative treatment OR osteopathic manipulative medicine OR osteopathic manipulative therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 3	3	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (cranial osteopathy OR craniosacral osteopathy OR craniosacral therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 2	40	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (manipulative medicine OR manual medicine OR manual therapy) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit
# 1	29	**TOPIC:** (heart rate variability OR hrv) *AND* **TOPIC:** (manipulation, chiropractic OR manipulation, musculoskeletal OR manipulation, orthopedic OR manipulation, osteopathic OR manipulation, spinal) *Indexes=SCI-EXPANDED, SSCI Timespan=All years*	Edit