The efficacy of Craniosacral Therapy for chronic neck pain

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“Gutta cavat lapidem, non vi sed saepe cadendo.”

“Water hollows the stone not through force but through constant dripping.”

Ovid

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Contents

1 Introduction ... 6
1.1 Neck pain ... 7
1.1.1 Theories of chronic pain ... 7
1.1.2 Classification and etiology of neck pain ... 9
1.1.3 Epidemiology and clinical course of neck pain ... 12
1.1.4 The treatment of neck pain ... 13
1.2 Craniosacral Therapy ... 15
1.2.1 Roots and rationale ... 15
1.2.2 Evidence of craniosacral mechanisms and clinical effectiveness ... 18
1.3 Research subject ... 19
2 Methods ... 21
2.1 Trial design and registration ... 21
2.2 Randomization ... 21
2.3 Sample criteria ... 21
2.4 Blinding ... 22
2.5 Interventions ... 22
2.6 Practitioner characteristics ... 23
2.7 Outcome measures ... 23
2.8 Data analysis ... 27
3 Results ... 29
3.1 Patient Recruitment and Flow ... 29
3.2 Sample characteristics at baseline ... 31
3.3 Concurrent treatments ... 32
3.4 Compliance with the allocated intervention ... 32
3.5 Treatment credibility and therapeutic alliance ... 32
3.6 Primary outcome ... 34
3.7 Secondary outcomes ... 37
3.8 Global improvement ... 39
3.9 Qualitative Outcomes ... 40
3.10 Safety ... 48

4 Discussion ... 49
4.1 Summary of evidence ... 49
4.2 Discussion of the study results ... 50
4.3 Explanation and translation of the treatment effects ... 52
4.3.1 Effects of treating fascial tissue ... 52
4.3.2 Effects of altering the autonomic nervous system response ... 53
4.3.3 Effects of emotion regulation ... 53
4.4 Methodological reflection ... 55
4.4.1 Trial design ... 55
4.4.2 Sample characteristics ... 55
4.4.3 Outcome measures ... 56
4.5 Strengths and weaknesses ... 58
4.6 Conclusions and further perspectives ... 58
5 Summary ... 59
7 References ... 60
8 Appendix ... 79
8.1 Index of abbreviations ... 79
8.2 List of figures ... 80
8.3 List of tables ... 81

1 Introduction

Neck pain is a common health problem with one in two people experiencing it at least once in their lifetime. Complaints of the neck area are often recurrent, non-specific in nature and associated with both social and occupational disability. For the treatment of chronic courses, clinical practice guidelines recommend manual therapies in combination with therapeutic exercise, cognitive-behavioral methods and complementary treatments such as acupuncture or yoga. In contrast, studies on pain medication provide evidence particularly in acute and subacute cases. Despite the available treatment options, recurrence rates of neck pain are still high. Reasons may include preferences for passive treatments, not guideline-compliant drug prescriptions, and the delay of combining treatments addressing both mechanical complaints and psychosocial risk factors.

Craniosacral Therapy (CST) is a complementary treatment that is thought to integrate both physiological and mental aspects of a patient. CST is a mindful, non-invasive treatment approach using gentle manual palpation techniques of fasciae between the cranium and sacrum. Initial clinical trials have shown that CST is effective for selected chronic pain syndromes but evidence is limited to observational designs and to randomized controlled trials of low to moderate methodological quality with generally high risk of performance bias. There is likewise only preliminary evidence that supports the inherent mechanisms of CST treatment techniques. Thus, it remains unclear how CST might work and whether pain alleviation is caused by: either specific treatment effects or placebo effects due to nonspecific responses associated with the treatment setting; with observation, assessment and interaction with the practitioner; or with the patients' expectations and prior experiences of the treatment.

This study therefore aimed to address the question about specific treatment effects of CST. For this purpose, a randomized sham controlled trial was developed to control for placebo effects and the risk of performance bias due to lacking patient blinding. In comparison to an active touch- and attention-control condition, CST should be tested for its efficacy in the treatment of chronic non-specific neck pain. Using additional qualitative methods should further contribute to the comprehension of therapeutic mechanisms and central domains of treatment response.

1.1 Neck pain

1.1.1 Theories of chronic pain

Since ancient times, human beings have developed theories of pain to deal with noxious stimuli they did not completely understand. In most primitive indigenous cultures, pain sensations were described within a mystical context using paraphrases of demons and spirits as sources for chronic pain (Müller-Busch, 2007). From Babylonian and Egyptian civilizations to the Christian Middle Ages, people similarly believed that pain was a god's judgment for human misconduct. To atone for sins, priests prescribed religious ablutions, prayers, and sacrifices. Pathophysiological studies of the human body or attempts at treating symptoms, however, were regarded as blasphemy. Previous philosophical approaches of Hippocrates, who described pain treatment as a recovery of the harmony of the humors and temperaments, were just as negated as the empirical approaches of Celsus and Galen, who had identified pain (dolor) as a diagnostic indication of local inflammation accompanied by heat (calor), redness (rubor), swelling (tumor), and loss of function (functio laesa) (Scott et al., 2004). Even da Vinci's anatomical studies and Paracelsus' entia theory, which integrated philosophical and astrological as well as alchemistic and physiological approaches, remained unpublished for decades as they contradicted the established doctrine.

With Descartes, pain became a more somatically conceivable phenomenon. Already in 1662, he postulated peripheral pain transmission to the brain by mechanistic traction of nerve endings resulting in protective reflexes. He was followed by Bell who discovered the differentiation of sensory and motor nerves in the spinal cord around 1800 and von Frey who proposed pain as an independent tactile quality that stimulated specific nerve endings in 1890 (Specificity Theory). In 1900, Goldscheider showed that repeated subthreshold tactile stimulation could be summarized to a perception of pain (Summation Theory) (Müller-Busch, 2007). However, as this pain perception was shown to be non-linear to the noxious stimulation and not exclusively explainable due to pain conduction from peripheral to central, Melzack and Wall (1965) developed the Gate-Control-Theory. They presumed that pain was modulated by afferent Aδ and C fibers as well as efferent neurons from cortical and subcortical areas causing descending inhibition of nervous conduction already at the dorsal horn of the spinal cord. The gate was hypothesized within the substantia gelatinosa where serotonergic and noradrenergic neurotransmitter activated interneurons, which in turn inhibited pain conduction from the first to the second neuron. In conditions of acute stress, high emotional arousal or huge injuries, nuclei of the brain stem and hypothalamus were able to completely mask pain perception via the release of serotonin, adrenalin, cortisol, and endogenous opiates. Peripheral inhibition on the other hand was modulated by fast Aβ fibers that were responsive to tactile stimuli and wide-dynamic range Aδ fibers that were innervated by noxious and thermal stimuli (Melzack, 1999; Mendell, 1966). This contributed much to the understanding of the mechanisms of manual therapies, acupuncture, and thermal treatments, which are shown to interfere with the slower noxious stimuli conducted via C and Aδ fibers (Melzack & Wall, 1989; Yu et al., 2013; Zusman & Moog-Egan, 2008).

The International Association for the Study of Pain summarized these findings into a new definition of pain. Pain was termed as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey et al., 1994, p. 210). With this definition, pain has become a more subjective perception, which is always associated with biological, affective, and social components and acts as a warning sign even if no tissue damage can be diagnosed. On the contrary, degenerative changes do not linearly relate to pain perception. Radiographic studies have shown that participants with chronic back pain and osteoarthritis have not significantly differed from the respective pain free parallelized control groups, as degenerative changes are highly prevalent in asymptomatic individuals as well (Boos et al., 1995; van Saase et al., 1989). The complex interactions of developing and maintaining chronic pain were first described by Engel (1977). He constructed a virtuous circle with positive feedback effects between: focused attention and selective perception (sensory discriminative components), evaluation (cognitive components), emotional arousal (affective components), sympathetic activation and hypervigilance (vegetative components), tone increase and protective tension (motor components), resting/avoiding/enduring reactions and passive coping (behavioral components), lowered pain thresholds, pain during movement, maladaptive cognitions, helplessness, anxiety/depression, and sleep problems (operant components), and social withdrawal and loss of positive reinforcement (social components). This self-sustaining process is modulated by an initial pain trigger, which can be of clearly physical origin, accumulate due to daily stressors, and/or be associated with traumatic experiences. As pain is evolutionarily associated with negative valence, nuclei of the formatio retikulis as well as areas of the anterior cingulate cortex assure the direction of attention towards the potentially dangerous stimuli. Sensory discrimination of pain location and intensity follows the lateral spinothalamic pathway to primary and secondary somatosensory cortices. Together with the insula, these areas are responsible for the integration of the different sensory components of pain perception. The following classification of the painful event as more or less controllable or threatening is executed by the prefrontal cortex depending on the situational context, the sociocultural background, and the individual learning history (Weiss & Schaible, 2008). As a result, emotions like fright, fear, despair, helplessness, or frustration can appear. Such affects are interconnected very quickly via subcortical pathways, particularly via the spinoreticular tract and medial/intralaminar nuclei of the thalamus, to the limbic system including areas of the gyrus cinguli and the amygdala and further innervations of secondary somatosensory and prefrontal regions, basal ganglia, and the periaqueductal gray (Weiss & Schaible, 2008). Along with the valence of an emotion, hypervigilance occurs in order to interrupt current behavioral patterns and avoid potential tissue damage. Respectively to the predominant emotion and the corresponding somatic marker (Damasio, 1996), hypothalamic structures stimulate the sympathetic nervous system and increase blood pressure, heart rate, respiration, and the hypothalamic-pituitary-adrenal axis. This state of increased tension and alertness initializes learned protection responses of fight or flight or, if both is not possible, freeze reactions (Alban & Pocknell, 2017; Porges, 2001). It can be followed by ongoing avoidance and resting behavior, further increases in myofascial tension and the development of negative operant and social moderators (Gatchel et al., 2007; Keefe et al., 2004). If no behavioral changes occur, neurophysiological processes of protection shift more and more towards chronification: functional plasticity then becomes structural with sustaining biochemical changes such as allodynia, primary and secondary hyperalgesia, peripheral and central sensitization accompanied by vegetative, hormonal, and motor dysfunctions (Tölle & Berthele, 2007; Woolf & Salter, 2000).

1.1.2 Classification and etiology of neck pain

Neck pain is defined as a symptom that may occur in relation to any disorder or disease above the shoulder blades. According to the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders the anatomic regions of the neck enclose the area from the linea nuchalis superior to the spina scapulae, the first thoracic vertebrae and the clavicula (Guzman et al., 2008). Pathoanatomical causes of neck pain can include osteoarthritis of the spinal joints, disc protrusion or herniations, trauma, whiplash, osteoporosis, or rheumatic diseases. Less common are tumors of the neck, infections of the nervous system, neural lesions due to central neuropathies or peripheral neuralgias, aneurisms, subarachnoid hemorrhages, or epidural hematomas (Childs et al., 2008). Indications of serious causes of neck pain are subsumed under the red flags including radicular symptoms, sensory or motor deficits, paresthesia, meningismus, consciousness disturbance, and headaches with concurrent vomiting, nausea, and vertigo (Scherer & Chenot, 2016).

However, the majority of the patients who present with complaints of the neck area are classified as having nonspecific/mechanical neck pain as no serious local pathology or systemic disease could be detected (Childs et al., 2008). Here, a multifactorial etiology is assumed with risk factors that increases the probability of developing neck pain and prognostic factors that decreases the probability of recovery from neck pain.

Socio-demographic factors:

Prospective cohort studies have shown that risk for neck pain development increases with age up to a peak in middle-age groups of between 35 and 49 and decreases in later life (Hogg-Johnson et al., 2008). Being in the middle years and having neck pain also seems to be a predictor for persistent neck pain 12 months thereafter (Hill et al., 2004). Evidence of the relationship between gender and neck pain varies. While men show partly higher incidence rates of specific neck pain, women have a greater risk for nonspecific neck complaints and more frequently use health care resources due to their neck pain (Hogg-Johnson et al., 2008). Cultural influences only appear to be of minor clinical relevance (Hogg-Johnson et al., 2008).

Prior pain and comorbidities:

A history of neck pain negatively predicted neck pain outcomes at 12 months (Bot et al., 2005; Croft et al., 2001). Prior low back pain and headaches were also identified as independent risk factors for the chronification of nonspecific neck pain (Croft et al., 2001; Hill et al., 2004).

Occupational factors:

Working conditions, moreover, can play an important role for neck pain development. Risk factors include sitting computer work, hard physical work, or working within the health care system (Jun et al., 2017; Yang et al., 2015), working more than 46 hours per week (Yang et al., 2015), low work task variation, high job demands, and competition instead of social support (Cote et al., 2008; Jun et al., 2017; McLean et al., 2010). Being off work was also found to independently predict persistent neck pain 12 months later (Hill et al., 2004).

Psychological and social factors:

There is consistent evidence for psychological factors as independent risk and prognostic factors for chronic nonspecific neck pain (Hogg-Johnson et al., 2008). Particularly as a result of maladaptive cognitions, pain patients experience helplessness and frequently tend to catastrophize normal bodily responses. This causes fear often accompanied by passive coping strategies, loss of positive reinforcements, avolition, hopelessness and depressive mood (Hasenbring et al., 2014; Keefe et al., 2004). Daily stressors and, with lower quality of evidence, stressful life events were also found to be linked to neck pain development and chronification (Linton, 2000). Furthermore, fMRI-studies have shown that in situations of loss, separation, or social exclusion, strong emotional reactions such as anger or grief are interconnected in approximately the same brain areas as those involved in physical pain processing (Eisenberger, 2012; Guendel et al., 2003).

Health behavior:

Behavioral factors associated with the chronification of neck pain include avoidance and resting, often accompanied by bad posture or insufficient physical activity due to fear of re-injury. On the other hand, neck pain patients tend to endurance behavior along with self-anesthetizing or ignoring their pain and not seeking professional health care (Bassols et al., 2002; Hasenbring & Verbunt, 2010; Hogg-Johnson et al., 2008; Linton, 2000).

Biochemical factors:

As a result of persistent pain and chronic muscle tension, biochemical changes can lead to plastic alterations within the neural, fascial, and muscular tissue. The ongoing stimulation of nociceptors provokes processes of peripheral sensitization and primary hyperalgesia leading to local nerve inflammation and restricted peripheral blood supply of the neck fasciae and muscles (La Touche et al., 2010; Le Bars, 2002). This in turn increases fascia and muscle tension (Langevin & Sherman, 2007; Stecco et al., 2014), compresses of nerves and vessels, and contributes to decreased pain thresholds (Johnston et al., 2008). Prolonged signal currents from peripheral nociceptors to wide dynamic range neurons of the spinal cord, moreover, can cause central sensitization and expansion of receptive fields (secondary hyperalgesia) with additional pain perceptions in adjacent areas of the neck (Woolf & Salter, 2000). Analog neuronal convergences are discussed for viscero-sensory afferences that refer pain to cervical segments of the spine from distant derma- and myotomes (Arendt-Nielsen et al., 2008; Henke & Beissner, 2011).

Irrespective of the specific or nonspecific circumstances surrounding the onset of neck pain the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders proposed a classification of four grades (Guzman et al., 2008):

1. Grade I neck pain: is associated with no signs or symptoms of major structural pathology nor minor interference with activities of daily living,
2. Grade II neck pain: shows no signs or symptoms of major structural pathology, but major interference with activities of daily living,
3. Grade III neck pain: shows no signs or symptoms of major structural pathology, but signs of a neurologic pathology,
4. Grade IV neck pain: presents signs or symptoms of major structural pathology.

The International Statistical Classification of Diseases and Related Health Problems (ICD) and the associated International Classification of Functioning, Disability, and Health (ICF) classified neck pain in impairment-based categories (Childs et al., 2008):

1. Neck pain with mobility deficits (ICD-10-M54.2: Cervicalgia and ICD-10-M54.6: Pain in the thoracic spine),
2. Neck pain with headaches (ICD-10-M53.0: Cervicocranial syndrome),
3. Neck pain with movement coordination impairments (ICD-10-S13.4: Sprain and strain of the cervical spine),
4. Neck pain with radiating pain (ICD-10-M46.2: Spondylosis with radiculopathy and ICD-10-M50.1: Cervical disc disorder with radiculopathy).

According to the duration of pain, neck pain is categorized as (Scherer & Chenot, 2016):

1. Acute neck pain with a duration of 0 to 3 weeks,
2. Subacute neck pain with a duration of 4 to 12 weeks,
3. Chronic neck pain with a duration of more than 12 weeks,
4. Recurrent neck pain with a symptom-free interval of no more than 4 weeks.

1.1.3 Epidemiology and clinical course of neck pain

Neck pain is common. The lifetime prevalence ranges between 14% and 71% suggesting a mean estimate of 48.5% of the adult population. In surveys of older people, the lifetime prevalence distributes around 17% (Fejer et al., 2006). The peak prevalences is consistently reported around the fifth decade of life; incidences are still increasing (Childs et al., 2008). It is estimated that between 10% and 21% are newly diagnosed with neck pain each year (Hoy et al., 2010). The global point prevalence is calculated as 4.9% (Hoy et al., 2014).

Although studies reported a 12 month-recurrence of 33% to 65% in patients suffering from an acute episode of neck pain, relapse rates are high (Hoy et al., 2010). Similar to low back pain, former neck pain episodes are predictive of both incidence and prevalence of future neck pain (Hogg-Johnson et al., 2008). Estimates of the neck complaints that will progress to recurrent or chronic courses range from 30% to 44% (Childs et al., 2008). Likewise, a systematic review of conservative treatments for chronic neck pain did not find significant reductions in pain scores for patients who were randomized to the control group receiving no specific treatment (Vernon et al., 2006). Disability due to neck pain is less common than that for low back pain. However, years lived with disability have continuously increased from 24 million in 1990 to 34 million in 2010 (Hoy et al., 2014) to 35 million in 2015. Among the 310 diseases analyzed in 2015, neck pain ranked as the second leading cause of disability in all higher and high-income countries (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016).

The economic burden of neck pain affects both direct and indirect costs of illness (Childs et al., 2008). In contrast to low back pain, patients with neck complaints do not seek health care in acute and subacute episodes of their neck pain. They tend to endure their neck pain until their symptoms become chronic (Guzman et al., 2008; Hasenbring et al., 2014). Chronic neck pain cases, however, significantly contribute to increased healthcare costs and work absenteeism (Cote et al., 2008; Mesas et al., 2014).

1.1.4 The treatment of neck pain

The treatment of chronic neck pain not associated with serious pathology can be challenging for both patients and therapists. Chronic neck pain patients often tend to consult multiple physicians, claim repeated diagnostic testing for supposed pathologic causes, and overdose on analgesic medication (Bassols et al., 2002; Haldeman et al., 2008). General practitioners similarly tend to prescribe drugs as the first-line therapy: beside non-steroidal anti-inflammatory drugs, even muscle relaxants and corticosteroids (Bassols et al., 2002; Vos et al., 2007), although the evidence on their clinical effectiveness and safety is inconsistent (Chou et al., 2004). Thus, the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders suggested focusing on modifiable risk and prognostic factors, in particular work, psychosocial and behavioral factors (Hogg-Johnson et al., 2008) rather than on passive strategies that are more likely associated with further chronification (Childs et al., 2008; Wong et al., 2016).

Standard treatments:

Clinical practice guidelines recommend oral drug treatment with nonsteroidal anti-inflammatory drugs for acute and subacute stages of nonspecific neck pain (Cote et al., 2016; Scherer & Chenot, 2016). Systematic reviews have shown safety and superiority compared to placebo (Wong et al., 2016). However, clinical relevance remains questionable, as nonsteroidal anti-inflammatory drugs were not found to be superior to any other non-pharmacological intervention for nonspecific neck pain (Hurwitz et al., 2008). Injections with local anesthetics also showed significant effects when compared to placebo (Peloso et al., 2007) but are not recommended by recent clinical practice guidelines because of possible serious adverse events (Scherer & Chenot, 2016).

Manual therapies such as manipulation and mobilization of the cervical and thoracic spine are recommended for acute, subacute, and chronic nonspecific neck pain cases (Childs et al., 2008; Scherer & Chenot, 2016). They appear to be more effective than sham treatment and showed greater short-term but no longer-term improvements in contrast to exercise sessions (Gross et al., 2015b; Hurwitz et al., 2008; Vincent et al., 2013). Combining manual therapies with therapeutic exercise revealed greater effects on neck pain intensity and disability than manipulation and mobilization alone (Cote et al., 2016; Hurwitz et al., 2008) and should be considered before prescribing drugs (Kjaer et al., 2017). With some limitations, clinical massage is also recommended for chronic nonspecific courses of neck pain, while relaxation massage is not (Cote et al., 2016; Kong et al., 2013; Patel et al., 2012).

The evidence on exercise alone varies (Gross et al., 2015a). Therapeutic range of motion and strengthening exercises were found to be effective in chronic neck pain patients up to two years after the intervention (Hurwitz et al., 2008). Workers who regularly exercised also showed better prognoses for recovery from neck pain (Cote et al., 2008). However, evidence from the general population suggested that physical activity may not be associated with decreased neck pain (Carroll et al., 2009) or may even lead to chronification in individuals with subacute neck pain who persist in performing strenuous physical exercises (Hasenbring et al., 2015). Thus, clinical practice guidelines recommend exercise as one component of multimodal care but conclude that physicians should not prescribe exercises as a single intervention for patients with chronic nonspecific neck pain (Cote et al., 2016).

International clinical practice guidelines also recommend psychological interventions as part of a comprehensive rehabilitation program for patients with chronic nonspecific neck pain (Cote et al., 2016; Scherer & Chenot, 2016). As single treatments, patient education, relaxation, and cognitive-behavioral therapy have shown inconsistent evidence (Gross et al., 2012; Monticone et al., 2015; Shearer et al., 2016).

Complementary therapies:

Patients with neck pain frequently use complementary therapies particularly to treat recurrent or chronic complaints (Clarke et al., 2016). Patients with acute episodes of neck pain more often request conventional primary care (Woodhouse et al., 2016). Clinical practice guidelines likewise recommend complementary treatments like acupuncture (Hurwitz et al., 2008; Scherer & Chenot, 2016), qigong exercises, or yoga (Cote et al., 2016) for chronic, but not for acute, nonspecific complaints of the neck. A recent meta-analysis found preliminary evidence that acupuncture is moderately more effective than no treatment (Furlan et al., 2012). However, results from acupuncture trials have shown high heterogeneity and often high risk of bias, also leading to negative recommendations (Cote et al., 2016). Evidence for qigong bases on two low risk of bias randomized controlled trials and confirms that qigong has greater benefits than waitlist (Southerst et al., 2016). A meta-analysis of yoga in chronic nonspecific neck pain patients revealed robust evidence for short-term effects of yoga in comparison to enhanced usual care for pain intensity, impairment, mood, and quality of life (Cramer et al., 2017). Patients who sustained yoga practice could even achieve long-term effects of up to twelve months (Cramer et al., 2013b).

Further complementary treatment approaches that showed preliminary positive effects in chronic nonspecific neck pain patients included cupping (Lauche et al., 2013), Alexander Technique in comparison to usual care but not to local heat application (Lauche et al., 2016; MacPherson et al., 2015), meditation (Jeitler et al., 2015), and individualized but not standardized osteopathy in comparison to sham (Klein et al., 2013; Schwerla et al., 2008). Physical therapists, asked about their perception of effective complementary approaches for the treatment of chronic pain conditions, most frequently recommended acupuncture, reflexology, aromatherapy, and Craniosacral Therapy (CST) (Hughes et al., 2011).

1.2 Craniosacral Therapy

1.2.1 Roots and rationale

CST has its origin in osteopathy, initially developed by A.T. Still (1828 – 1917). After the death of three of his children, he began to investigate the human anatomy and physiology seeking causes of disease beyond those provided by the conventional medicine of his day (Trowbridge, 1991). Still describes disease as an expression of the body’s restricted ability for self-regulation. By manipulating physical structures, he intended to correct acquired dysfunctions, which in turn, he believed, would enhance self-regulating bodily forces. With this salutogenic approach Still proposed a different philosophy to the equally upcoming, but more pathologically focused model of chiropractic care (Trowbridge, 1991).

W.G. Sutherland (1873 – 1954), one of Still’s students, proposed the cranial concept in osteopathic medicine. In his early heuristic studies, he observed inherent movements of the cranial bones and concluded that the hypothesis of the ossification of the sutures of the adult skull has to be wrong (Magoun, 1997). This contradicted the scientific consensus of the British and American anatomical associations. However, in 1923, Italian anatomists had already postulated the immobility of the cranial sutures as a pathological abnormality rather than as a developmental step (Testut & Sperino, 1923, quoted from Upledger & Vredevoogt, 1983). Newer histological studies, reviewed by Green et al. (1999), revealed supportive evidence for Sutherland's concept of cranial bone mobility although it is noted that its therapeutic impact remains questionable. The authors also reviewed studies examining different tidal rhythms of the cerebrospinal fluid, a further observation of Sutherland's research. They deduce that: current evidence supports the ability to measure craniosacral rhythms or impulses distinctly from other body rhythms such as respiration or cardiac activity using encephalogram, myelogram, and magnetic resonance imaging (Green et al., 1999). Sutherland described these rhythms as a function of the mobility of the brain and spinal cord, the fluctuation of the cerebrospinal fluid, the mobility of the dural tube as well as of the mobility of the cranial bones and the sacrum between the ilia (Magoun, 1997).

In the 1970s, J.E. Upledger (1932 – 2012) in turn observed a pulsation of the spinal dural tube during a tumor removal surgery. He reported that he was unable to interrupt the rhythmic motion, which complicated the operation. At that time, none of the treating neurosurgeons had an explanation for this anomaly. Upledger then participated in a cranial osteopathy training and was shown to palpate the motion of the cranial bones, which reminded him of the pulsation of the dural tube, he observed during the surgery a few months before (Upledger, 1997). He continued to research the craniosacral rhythms and the related fascial system and established CST as a treatment approach distinct from osteopathy in 1983. While both the craniosacral and the osteopathic concept utilize gentle manual palpation techniques to release restrictions of the myofascial and skeletal system, one of the biggest differences consists in the way of dealing with tissue resistance (Upledger & Vredevoogt, 1983).

Osteopathic medicine usually consists of forced mobilization and manipulation techniques, whereas CST techniques aim to be more non-invasive by touching not exceeding tissue resistances (Kuleßa, 2017). Too invasive therapeutic stimuli are thought to reinforce existing and provoke protective resistances, which may inhibit adaptive physiological processes. In 1899, the psychologist R. Arndt and the pharmacologist H.P.F Schulz described similar processes. Based on Paracelsus' "sola dosis facit venenum" ("the dose makes the poison") the Arndt-Schulz rule stated that for any substance: small doses stimulate self-regulation, moderate doses inhibit self-regulation, and large doses terminate self-regulation (Stumpf, 2006). Newer research on somato-autonomic reflexes, which describes associations between somatic stimulation and alterations in the autonomic nervous system (Uchida & Budgell, 2009), may contribute to the understanding how invasive manual techniques might inhibit regulative physiological processes and promote symptom chronification. It is assumed that straining a muscle beyond the normal degree of tissue resistance is a physical stressor in itself.

It will result in sympathetic activation and increased muscle tension in preparation for a subsequent stimulus. Conduction via subcortical pathways to the brain then mediates whether or not this stressor is interpreted as a positive training impulse or a potential risk of repeated injury and pain. Upon further strain or stretching, chronic pain patients, in contrast to healthy individuals, habitually respond with further increasing sympathetic arousal (Kingston et al., 2014), while muscle tension temporarily decreases. Giving up muscle resistance during high neural arousal, however, is associated with a parasympathetic immobility or freeze response (dorsal vagal mode) rather than parasympathetic relaxation (ventral vagal mode) (Keay et al., 2000; Porges, 2001) and the experience of not being adequately prepared against the external stressor. With repeated manipulation, muscle tissue can become pathologically tense. The texture of fasciae was discussed as an additional factor that might contraindicate manipulative techniques. Beside its proprioceptive properties and key role in preparing for muscular activity (Benjamin, 2009; van der Wal, 2009), the continuity of fascia also between distant body regions makes them less flexible than muscle fibers and more vulnerable against micro injuries and inflammation, fibrosis and rigidity (Chaudhry et al., 2007; Langevin & Sherman, 2007; Stecco & Day, 2010). Even Cochrane reviews have shown greater short-term than long-term effects for various manipulative therapies (Gross et al., 2015b; Walker et al., 2011). Upledger, on the other hand, developed several indirect palpation techniques anatomically linked to the ventral vagus in order to support the patient's body to switch into the relaxing parasympathetic mode. This should foster oxytocin secretion and feelings of being safe, settled and calm (Morhenn et al., 2012; Porges, 2001). He further used gentle fascial traction, release, and unwinding techniques that follow, but did not break, tissue resistances. This should promote the body's experience of release as a successful concept in dealing with pain (Minasny, 2009; Upledger & Vredevoogt, 1983).

The second difference from osteopathy is the idea of not limiting diagnostic and therapeutic procedures to the physical body but integrating emotional aspects as well. Upledger developed his approach of somato-emotional release during his work with autistic children (Upledger, 1990). When the children were relaxed and gravity was removed by gently holding their limbs, he observed spontaneous involuntary bending, rotating, and unwinding motions of the respective body parts in rhythmic or chaotic patterns (Minasny, 2009), often accompanied by rapid eye movement and deep breathing (Bertolucci, 2008). If Upledger followed through these motions without fostering them, he often observed a kind of terminal point where the treated limbs stopped moving. At this point, the children usually responded with relaxation of fasciae and muscles, often accompanied by emotional release conveying fear, frustration, or anger. Afterwards, the autistic children showed more peaceful facial expressions, more social contact and less self-destructive behavior (Upledger, 1990). In his work with adults, Upledger described emotional release during specific body postures. These often coincided with emerging memories of initial physical traumata (Upledger, 1990). Recent basic research on suppressed emotions and state-dependent memories (Anderson et al., 2004; Depue et al., 2007) provide preliminary support for Upledger's theory of somato-emotional release. Thus, emotional memories could be triggered much easier by similar than any other circumstance or posture, by which they had been originated. As Upledger (1990) was aware that exposing a patient to conditions related to an initial trauma is potentially re-traumatizing, he emphasized the need to simultaneously treat the patient's nervous system, decrease the sympathetic hyperarousal and establish a safe environment for ventral vagal activation according to Porges (2001). With this technique, Upledger described having achieved a sustaining release of muscle tone and protective tension in addition to emotional re-organization – two processes that he considered as being often mutually dependent in patients with chronic or recurrent pain (Upledger, 1990).

1.2.2 Evidence of craniosacral mechanisms and clinical effectiveness

The first scientific review and critical appraisal of the evidence on CST was published in 1999 by researchers at the University of British Columbia, Canada (Green et al., 1999). This Health Technology Assessment found evidence from nine histological studies that supported the mechanisms of cranial bone motion; and from eleven studies conducted outside the field of complementary medicine that measured different rhythmic craniosacral flow patterns by encephalogram, myelogram, and magnetic resonance imaging. However, the quality of evidence showing any relation between bone restrictions or pathophysiological rhythmic fluid activity and health outcomes was considered very week. In addition, the authors could not found any reliability of different examiners' assessments of craniosacral fluid patterns (Green et al., 1999). In contrast, newer studies have revealed preliminary evidence for significant intra-class correlation coefficients for examiners palpating the same anatomic structure but equally poor to nonexistent inter-examiner reliability for simultaneous palpation of the head versus the sacrum (Halma et al., 2008; Moran & Gibbons, 2001).

With respect to the use of complementary therapies in patient populations, only a few epidemiological surveys initially searched for CST. Studies from the United States and the United Kingdom reported CST use in patients with musculoskeletal complaints of the back and neck, headaches and migraine, dizziness and tinnitus, gastrointestinal disorders as well as stress-related and mental problems like depression and anxiety (Harrison & Page, 2011; von Peter et al., 2002). Further examinations found that CST is frequently sought by parents to treat their children's complaints. Highest rates of use are reported for neurological infants, followed by respiratory, oncological, allergic, and gastroenterological pediatric diseases (Hurvitz et al., 2003; Low et al., 2008). United Kingdom NHS cancer centers (Gage et al., 2009) and Swiss psychiatric university hospitals (Stocker, 2009) has established treatment concepts that integrate CST as a complementary approach to conventional care.

The effectiveness of CST in improving pain intensity and health-related quality of life has been shown for a number of chronic pain syndromes, but is limited to observational designs and randomized controlled trials with only low to moderate methodological quality (Green et al., 1999; Jäkel & von Hauenschild, 2012; Tan et al., 2007). Beside the overall unclear risk of selection and detection bias due to poor reporting, the risk of performance bias remains high for all of the reviewed studies, as patients were not blinded to treatment allocation. This raises the question about the extent of specific treatment effects of CST, also because non-pharmacological therapies are shown to induce greater placebo effects than single drug treatments (Hrobjartsson & Gotzsche, 2010).

1.3 Research subject

Recent placebo research on CST is mainly limited to non-manual sham conditions using ineffective physical devices (Castro-Sanchez et al., 2011; Mann et al., 2008; Mataran-Penarrocha et al., 2011). Secondary analyses of these non-manual sham interventions in comparison to CST did not reveal comparable levels of expectancy (the patients' preconceptions about their improvement from treatment) nor credibility (the patients' beliefs about the treatments' rationale for managing their condition) (Curtis et al., 2011). This may decisively impact effect sizes, as several pain studies have found that higher values of both expectancy and credibility significantly predict higher improvements on study outcomes (Kalauokalani et al., 2001; Myers et al., 2008; Smeets et al., 2008). Likewise, the interaction between patient and practitioner has been shown to influence the overall treatment effect depending on how the patient rated the alliance quality (Goldstein et al., 2002). When using an ineffective physical device, controlling for effects of attention, empathy, and even touch is not feasible.

A valid placebo for randomized controlled trials should therefore mimic CST with regards to treatment duration, frequency, procedure, and therapist attention (Miller & Kaptchuk, 2008; Price et al., 2008; Staud, 2011). To control for mechanisms of classical and operant conditioning, patients' levels of expectancy and credibility should be assessed and included in statistical analyses as well (Benedetti et al., 2003). Sham designs for manual therapy trials used several forms of manual placebos including gentle manipulation, effleurage, soft tissue massage, or mild acupressure (Ernst & Harkness, 2001; Hawk et al., 2005; Noll et al., 2004; Vernon et al., 2005; Yeung et al., 2012). In a CST asthma study, a light touch sham treatment has been used but not been tested as credible (Mehl-Madrona et al., 2007).

For patients suffering from chronic neck pain, no efficacy studies have been conducted to date, although neck and back pain are the most frequent complaints for which CST is requested (Harrison & Page, 2011). Therefore, we developed a two-arm randomized controlled design for patients with chronic nonspecific neck pain that compared CST to light touch sham treatment. We tested it for its credibility and success in blinding patients to group allocation, which should allow analyzing specific CST treatment effects in contrast to those of an active touch- and attention-control condition. In addition, we used qualitative methods to investigate therapeutic mechanisms of CST and central domains of the treatment response.

2 Methods

2.1 Trial design and registration

The study was designed as a randomized controlled mixed-methods trial in accordance with the CONSORT (Schulz et al., 2010) and COREQ (Tong et al., 2007) guidelines. After baseline assessment, patients were randomized into either the CST group or an active attention-control group receiving light-touch sham treatment. Outcome measures were collected at week 8 after randomization (post intervention) and week 20 after randomization (3-month follow-up). The trial was conducted between February 2012 and May 2013 at the Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, University of Duisburg-Essen, Germany. Before patient recruitment, the trial protocol was approved by the ethics committee of the University Hospital Essen, Germany (11-4850-BO), and registered at ClinicalTrials.gov (NCT01526447). No external funding was received for this study.

2.2 Randomization

A statistician, who was not involved in conducting the study, generated a non-stratified random allocation sequence with randomly varying block lengths using the random number generator RANUNI from the SAS/STAT software (release 9.2, SAS Inc.). On the basis of these random number tables, he prepared sealed and opaque envelopes sorted in the ascending order of randomization. To reveal the patients' group assignment, the envelop with the lowest number was opened directly after each baseline assessment by the trial coordinator who was neither involved in the random sequence generation nor in the assessment of study outcomes.

2.3 Sample criteria

Patients were recruited from specialist care, primary care, and non-care populations through advertisements. To assess eligibility, those who called in were screened by a research assistant, whereupon eligible patients obtained written study information and a physical and neurological examination by a study physician. If all eligibility criteria were met, patients had to give written informed consent and were included in the study. Inclusion criteria were: age between 18 to 65 years, chronic nonspecific neck pain for 3 months or more with a moderate pain intensity of at least ≥ 45 mm on a 100-mm visual analog scale (VAS) ranging from 0 (no pain at all) to 100 (worst possible pain) (Jensen et al., 2003), and treatment naivety with respect to CST. Participation was not possible in cases of specific neck pain due to degenerative diseases (disk prolapse, scoliosis), inflammatory diseases (spondylitis, arthritis), neurological diseases (neuropathy, multiple sclerosis), physical traumata (whiplash, operation of the cervical spine), or neoplasms of the spine. Severe comorbid somatic and psychiatric disorders such as oncological diseases or major depression and current pregnancy were exclusion criteria, too. Patients taking corticosteroids, opiates, muscle relaxants, antidepressants, or those with recently initiated or modified drug therapy or invasive/manipulative treatment were also excluded.

The sample size was calculated from pain intensity ratings of chronic nonspecific neck pain patients receiving osteopathic manipulative treatment (Schwerla et al., 2008) using the G*Power software (release 3.1.3, Kiel University, Germany). To detect an expected group difference with a standard deviation (SD) of 1.73 ± 2.16 on a 10-point numeric rating scale (effect size of 0.84) with 80% of power, a two-sided t-test with a 5% significance level required 24 patients per group. To account for a possible loss of statistical power due to patient dropout of 10%, a total sample size of 54 was calculated. For the qualitative analyses, a consecutive sampling strategy was chosen including all accessible subjects of the CST group that agreed to participate in the interview (Gibbs et al., 2007).

2.4 Blinding

Firstly, patients were blinded to group allocation and to the fact that one group would receive sham treatment, as recommended for manual therapy trials (Bialosky et al., 2011); instead they were told that different CST approaches would be tested. Secondly, outcome assessors remained blind to patients' group allocation during the whole study period. Thirdly, the statistician who conducted quantitative analyses was blinded to group allocation by renaming groups with numbers.

2.5 Interventions

For both groups, standardized treatment protocols comprised eight individual units of CST or sham treatment once a week lasting 45 minutes each (Mann et al., 2008). All patients received an initial structural CST examination including: assessment of recent symptoms, general and local listening for connective tissue restrictions, and evaluation of the craniosacral rhythm. Treatment steps were recorded by therapists using a structured log.

The CST protocol was designed to release palpated restrictions of the cranium and the spine up to the pelvis and the sacrum using standardized application of gentle fascial traction, release, and unwinding techniques in accordance with the respective palpated restrictions (Koes, 2004; Mann et al., 2008). Selected CST techniques included: frontal and parietal lift, medial compression of the parietal bones, compression-decompression of the sphenobasilar and the temporomandibular joints, release of the sagittal suture and the atlanto-occipital joint, cranial base release, release of the hyoid diaphragm and the thoracic inlet, dural tube traction, respiratory and pelvic diaphragm release, lumbosacral and sacroiliac decompression, and fascial unwinding of the neck and shoulders. Still point induction, a technique to temporarily suspend the craniosacral rhythm, complemented the CST protocol (Minasny, 2009; Upledger & Vredevoogt, 1983). If indicated, dialog techniques for increasing body awareness and assisting the process of somato-emotional release were used (Upledger, 1990).

The sham protocol was designed to be credible but not specifically effective. Therefore, light touch was applied on standardized anatomic areas equal to those treated with CST, for 2 minutes duration each (Mehl-Madrona et al., 2007; Noll et al., 2004). In addition, body awareness instructions were given to simulate CST dialog techniques.

2.6 Practitioner characteristics

In contrast to other CST studies (Mann et al., 2008; Mataran-Penarrocha et al., 2011), more than one therapist took part in treating patients, despite the fact that weak inter-rater reliability has been reported for craniosacral assessment techniques (Hanten et al., 1998; Moran & Gibbons, 2001; Sommerfeld et al., 2004). The multi-therapist design was chosen with respect to higher generalizability, intending to evaluate the therapy effect, not the therapist effect. Thus, three practitioners were selected to perform the CST treatments and one additional therapist for the sham treatments. All were female, licensed CST therapists with on average 6 years of clinical practice. Moving patients between therapists was not envisaged, because of possible dilution of study effects (Mehl-Madrona et al., 2007).

2.7 Outcome measures

The primary outcome was average pain intensity during the last 7 days, recorded on a 100-mm VAS at week 8 (Hjermstad et al., 2011). Secondary outcomes included: pain on movement, pressure pain sensitivity, neck pain-related disability, health-related quality of life, well-being, anxiety, depression, stress perception, pain acceptance, body awareness, patients' global impression of improvement, and safety.

To assess pain on movement, patients filled in the Pain on Movement Questionnaire and were asked to rate their pain intensity on a 100-mm VAS while flexing, extending, laterally flexing, and laterally rotating their head. The average pain score was then calculated from all movement directions (Lauche et al., 2014b). Pressure pain sensitivity was measured at the individual point of maximum pain and bilaterally at anatomically predefined sites (levator scapulae, trapezius and semispinalis capitis muscle). For these points, pressure pain thresholds (PPT) were determined 3 times each using a digital algometer (Somedic AB, Hörby, Sweden) with a 1-cm^2 cylinder. Pressure was applied in steps of 40 kPa/s until patients reported pain in addition to pressure (Cramer et al., 2013c; Johnston et al., 2008). Functional disability was assessed using the Neck Disability Index (NDI), a 10-item questionnaire that measures the disabling effect of neck pain on activities of everyday life. Scores of < 9 indicate no perceived disability, 10 to 29 mild disability, 30 to 49 moderate disability, 50 to 69 severe disability, and 70 to 100 complete disability (Cramer et al., 2014). Health-related quality of life was assessed on two subscales, physical and mental quality of life, using the 12-item Short Form Health Survey (SF-12). Subscales were standardized to a mean of 50 ± SD of 10 and a range of 0 to 100, with 0 indicating the lowest level and 100 the highest level of health (Jenkinson et al., 1997). Well-being was measured by the mean score of the 16-item Questionnaire for Assessing Subjective Physical Well-being (FEW), which assessed stress resilience, vitality, inner peace, and the ability to enjoy on a rating scale of 0 (strongly disagree) to 5 (strongly agree) (Albani et al., 2006). Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). Each subscale is composed of seven items with a maximum of 21 points. Scores below 8 indicated anxiety and depression levels within normal levels, 8 to 10 points indicated subclinical levels, and over 10 points a possible clinical disorder (Herrmann, 1997). To assess stress perception, patients obtained the Perceived Stress Questionnaire (PSQ) in the 20-item version ranging from 0 (lowest stress level) to 100 (highest stress level) (Fliege et al., 2005). Pain acceptance was measured by the mean score of the Positive Life Construction Scale of the Emotional/Rational Disease Acceptance Questionnaire (ERDA) comprised of 8 items that have to be answered on a rating scale from 1 (does not apply at all) to 4 (applies very much) (Büssing et al., 2008). Body awareness was measured by the Scale of Body Connection, which is composed of two subscales: body awareness and body dissociation. Results are displayed as means ranging from 0 (lowest body awareness/ dissociation) to 4 (highest body awareness/dissociation) (Price & Thompson, 2007). Patients' ratings of their Global Impression of Improvement (PGI-I) were assessed on a rating scale from 1 (very much improved) to 7 (very much worse) (Guy, 1976; Hudson et al., 2009).

Safety assessment was ensured by a study physician and the treating therapists who documented all adverse events. Patients were asked at the beginning of each treatment unit and at week 8 after the intervention about the frequency and the severity of adverse events. In addition, patients were requested to document adverse events as well as concurrent treatment and medication use in a daily log. Adverse events were defined according to the Good Clinical Practice Guidelines as any untoward medical occurrence in a treated patient and which does not necessarily have a causal relationship with the examined treatment (European Medicines Agency, 2002). Serious adverse events were defined accordingly as any untoward medical occurrence that require inpatient hospitalization, resulted in significant, life-threatening disability or death.

Moreover, treatment expectancy and credibility were assessed by the adapted Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000; Smeets et al., 2008) with a rating scale from 1 (not at all) to 9 (very much). Three of the originally six items were selected to measure: treatment expectancy, consistency of the treatment and willingness to recommend the treatment to a friend (Curtis et al., 2011). A post hoc principal component analysis confirmed the original two-factor solution, which confirmed for the expectancy item higher loadings on the factor treatment expectancy (0.99); and for the consistency and recommendation items higher loadings on the factor treatment credibility (0.96 for both items) (see appendix). While patients' expectancy of clinical improvement from CST was assessed before randomization, credibility items were part of the post intervention assessment. At week 8, patients were also administered the Helping Alliance Questionnaire (HAQ) (Luborsky et al., 1996) to evaluate the quality of the relationship between patient and therapist and control for attention effects. It comprised of a valid and reliable adaption of 11 items that were answered on a rating scale from 1 (strongly disagree) to 6 (strongly agree) (Bassler et al., 1995). Values were summarized to two subscales: quality of the therapeutic alliance and treatment satisfaction. To assess the compliance with the allocated treatment, the number of the attended units and the reasons for non-attendance were recorded.

Qualitative outcomes were assessed by semi-structured interviews (Mayring, 2002) on the basis of body image drawings (Figure 1) (Cramer et al., 2013a). Patients were asked to complete the missing body outlines and areas of pain and tension as perceived during a short guided imagery of the neck and upper back both before and after the 8 weeks of treatment.

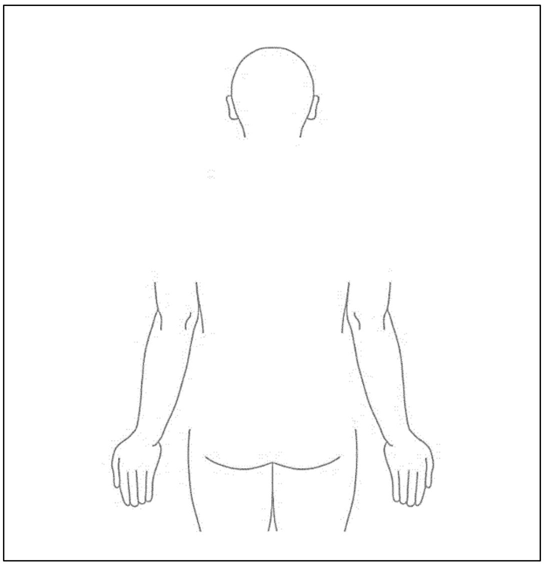

Figure 1. Template of the body image drawing

Table 1. Semi-structured interview guide

Topic	Main questions	Further questions
Drawings	– I would like to invite you to describe your present drawing. – To what extent do you see similarities and differences in comparison to your drawing before the CST treatment?	– What meaning do you ascribe to the colors you used? – To what extent do these differences have clinical relevance for you?
Pain and related physical responses	– To what extent did you perceive changes in your pain intensity or pain perception after the CST treatment? – To what extent did you perceive further physical responses to CST treatment?	– When did you recognize these changes for the first time? – How do you perceive your neck area right now?
Changes in body perception	– How did you perceive your neck area in relation to other body parts before treatment? – How far has this relation changed?	– To what extent have you perceived further changes in the way your body feels?
Effects on mood and mind	– To what extent did you experience changes in your mood during or after the treatment with CST? – To what extent did the treatment affect your mind/your way of thinking about yourself and your chronic pain?	– To what extent did you experience strong emotions such as crying, fear or happiness? – To what extent did you experience autobiographical memories during the therapy?
Behavioral implications	– To what extent have you learnt new strategies for dealing with your pain?	– To what extent have your coping strategies changed up to today?
Socio-economic burden	– To what extent have you experienced changes in your family/social life or at work?	– To what extent have your relatives noticed changes due to the CST treatment?
Safety	– To what extent did you perceive CST as unpleasant or painful?	– How would you assess those side effects in relation to the treatment effects?

Subsequent to the second drawing at week 8, CST patients were interviewed according to a previously developed interview guide (Table 1) on the meaning and contrasts of the drawings and the effects of CST on pain intensity and perception, and related physical, mental, behavioral, social, and economic outcomes. Additional open-ended questions on each topic were optional. Interviews were conducted face-to-face by a female psychologist with advanced training in qualitative research methodology and experiences in CST.

2.8 Data analysis

All quantitative analyses were based on the intention-to-treat population including all patients initially randomized, regardless of whether they had missing data or had not fully adhered to the treatment protocol. For randomized trials, intention-to-treat analysis is recommended over a per-protocol analysis as it controls for systematic bias, for instance due to withdrawal of patients with less positive treatment effects or increased adverse events (Moher et al., 2001). Missing values were imputed 20 times using fully conditional specification iterations, a multiple imputation technique based on multivariate regression models of baseline values and sociodemographic parameters (Schafer, 1997; White et al., 2011). Dropout analyses and baseline comparability were analyzed using independent-samples t-tests for continuous data and chi-squared tests for categorical data. Data on concurrent use of analgesics were converted into defined daily doses (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2013) and analyzed using repeated measures analysis of covariance with the treatment group as the classified factor and patients' expectations as the linear covariate. Use of other concurrent treatments was analyzed descriptively. Patients' compliance with the respective study condition was analyzed by independent samples t-tests.

The primary outcome was analyzed as a function of the treatment group (classified factor), patients' expectations, and respective baseline values (linear covariates) using univariate analysis of covariance. Between-group differences (Δ) and 95% confidence intervals (CI) were estimated using two-sided t-tests, and an alpha level of 5%. Equal covariance models were applied for secondary outcomes and patients' global impression of improvement, which is often considered as a categorical variable but has already been analyzed as a continuous scale (Twiss et al., 2007). All secondary analyses were planned as exploratory analyses. This way, no alpha-level adjustment for multiple testing was necessary (Feise, 2002). For each outcome, standardized effect sizes (Cohen's d) were calculated by dividing estimated group differences by the pooled SD at baseline (Cohen, 1988). In addition, responder analyses were calculated for patients who improved by at least 20% of their respective baseline values (minimal clinically important difference) and for patients with at least

50% improvement (substantial clinical benefit) (Dworkin et al., 2008; Kovacs et al., 2008). Between-group differences for treatment response analyses were tested with chi-squared tests. Data on tolerability and safety were analyzed descriptively.

To test the credibility of the sham protocol, a non-stepwise logistic regression model (enter method) was applied on the group variable with treatment expectancy, treatment consistency, treatment recommendation, alliance quality, and treatment satisfaction as independent continuous predictors. Adjusted odds ratios (AORs) and 95% CIs were calculated to assess whether treatment group could be predicted from included variables. The Hosmer-Lemeshow goodness-of-fit test was used to assess how well the chosen model fits the data. Logistic regression was carried out on both the per-protocol dataset (all cases with complete data) and the pooled dataset (intention-to-treat population). Quantitative analyses were performed using the SPSS software (release 22.0, IBM).

Interviews were audio-recorded, anonymized and professionally transcribed verbatim. Qualitative data were coded independently by three coders using MAXQDA software (Version 11.0.9, VERBI). As a first analysis, word frequencies were calculated across all transcripts by excluding interviewer sections and irrelevant words in patients' quotes. Graphical execution was realized using WORDLE™ software. Codes were then summarized to themes and subthemes, paraphrased and translated into English by an interdisciplinary interpretation group of physicians, psychologists, physical therapists and cultural scientists using inductive qualitative content analysis (Mayring, 2002). An inductive approach is thereby characterized by identifying themes that are related to the interview data themselves. Each theme was finally linked-back to the patient's original quote, by use of the patient's randomization number and the cited paragraph within the respective transcript. As no back-translation from English to German was performed (ideally accomplished by an external translator who has not been involved in the analysis process), cited original German quotes can be found in the appendix as well.

3 Results

3.1 Patient Recruitment and Flow

Figure 2 shows the Consort flow chart of patient recruitment and loss during the study period. Out of 150 prospective patients, 96 had to be excluded because they either did not fulfill the eligibility criteria (n = 86), or for reporting scheduling problems (n = 5). In total, 54 patients were randomly allocated to the treatment groups. Whereas four patients from the CST group and eight patients from the sham group did not attend all treatment units provided, only three patients were lost to assessment at week 8. Reasons for dropout were scheduling problems and loss of interest. At week 20, seven patients dropped out due to scheduling problems, and two others made no further contact. Comparisons of patients who completed the study with those who were lost to week 8 and week 20 revealed no significant differences concerning their social demographics, neck pain characteristics, and treatment expectancy (p ≥ .05) (Table 2). The subsample for the qualitative analyses included n = 20 of the 27 patients of the CST group. Compared to the seven withdrawn patients, also no significant differences in social demographics, neck pain characteristics, or treatment expectancy were found (p ≥ .05) (Table 3).

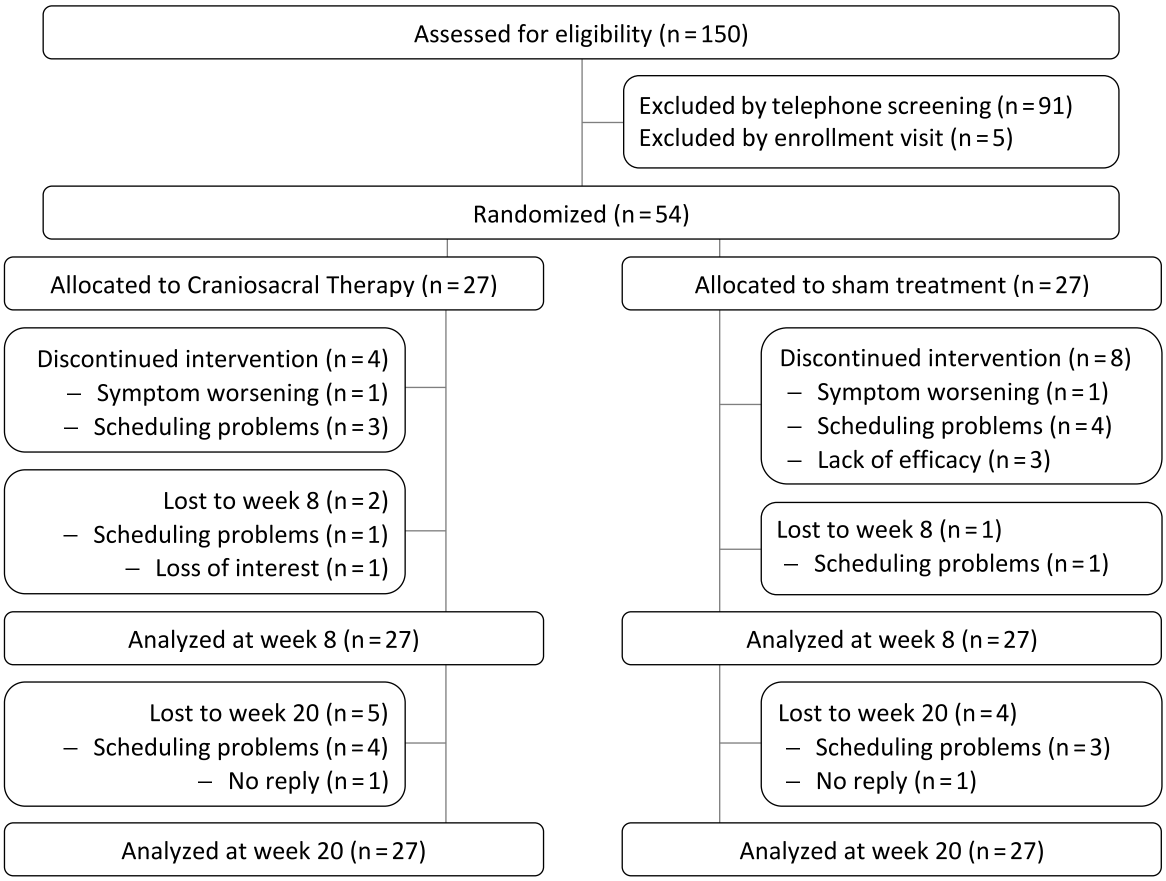

Figure 2. Consort flow chart

Table 2. Quantitative data: drop-out analysis

	Completed week 8 (n = 51)	Lost to week 8 (n = 3)	P
Age (years) (mean ± SD)	44.8 ± 10.1	40.3 ± 8.3	.455
Gender (female|male) (%)	80.4|19.6	100|0	.390
Education (<high school|high school|university) (%)	34.0|34.0|32.0	33.3|66.7|0	.553
Employment (unemployed|employed|pensioned) (%)	3.9|92.2|3.9	0|100|0	.881
Duration of pain (years) (mean ± SD)	9.9 ± 9.1	4.6 ± 4.6	.328
Pain intensity at baseline (VAS) (mean ± SD)	64.5 ± 13.2	60.0 ± 0.66	.560
Treatment expectancy (CEQ) (mean ± SD)	6.8 ± 1.3	6.7 ± 1.2	.878

Abbreviations: CEQ: Credibility/Expectancy Questionnaire; SD: Standard deviation; VAS: Visual Analogue Scale.

Table 2. Quantitative data: drop-out analysis (continued)

	Completed week 20 (n = 45)	Lost to week 20 (n = 9)	P
Age (years) (mean ± SD)	44.7 ± 10.4	44.3 ± 8.7	.920
Gender (female|male) (%)	79.5|20.5	90.0|10.0	.442
Education (<high school|high school|university) (%)	29.5|34.1|36.4	55.6|44.4|0	.143
Employment (unemployed|employed|pensioned) (%)	4.5|93.2|2.3	0|90.0|10.0	.411
Duration of pain (years) (mean ± SD)	9.5 ± 9.0	10.0 ± 9.3	.889
Pain intensity at baseline (VAS) (mean ± SD)	64.4 ± 13.5	63.8 ± 10.6	.898
Treatment expectancy (CEQ) (mean ± SD)	6.8 ± 1.3	6.7 ± 1.4	.833

Abbreviations: CEQ: Credibility/Expectancy Questionnaire; SD: Standard deviation; VAS: Visual Analogue Scale.

Table 3. Qualitative data: drop-out analysis

	Completed interview (n = 20)	Lost to interview (n = 7)	P
Age (years) (mean ± SD)	43.4 ± 6.9	47.4 ± 10.4	.313
Gender (female|male) (%)	70|30	71.4|28.6	.943
Education (<high school|high school|university) (%)	25|30|45	57.1|28.6|14.3	.231
Employment (unemployed|employed|pensioned) (%)	10|90|0	0|85.7|14.3	.168
Duration of pain (years) (mean ± SD)	9.9 ± 9.3	10.1 ± 9.6	.958
Pain intensity at baseline (VAS) (mean ± SD)	6.4 ± 1.4	6.4 ± 0.8	.893
Treatment expectancy (CEQ) (mean ± SD)	7.2 ± 0.9	6.6 ± 1.5	.267

Abbreviations: CEQ: Credibility/Expectancy Questionnaire; SD: Standard deviation; VAS: Visual Analogue Scale.

3.2 Sample characteristics at baseline

Patients' baseline characteristics are shown in Table 4. Their age ranged from 19 to 65 years, with a mean of 44.6 ± 10.0 years. Most were female (81.5%), employed, and of normal body mass index. The sample included an equal distribution of patients from all educational levels. Patients reported 9.6 ± 8.9 years of neck pain duration. During that time, most of them had received several pharmacological and non-pharmacological treatments. No significant differences in patients' social demographics and neck pain characteristics were found between study groups ($p \geq .05$). Patient's expectations that CST would be successful in reducing their neck pain symptoms were also comparable between groups ($p \geq .05$).

Table 4. Sample characteristics at baseline

	Craniosacral Therapy (n = 27)	Sham (n = 27)	P
Age (years) (mean ± SD)	44.2 ± 9.7	45.0 ± 10.5	.769
Gender (female|male) (%)	70.4|29.6	92.6|7.4	.076
Body mass index (kg/m^2) (mean ± SD)	24.5 ± 4.3	25.5 ± 5.0	.461
Education (<high school|high school|university) (%)	33.3|29.6|37.1	34.6|42.3|23.1	.153
Employment (unemployed|employed|pensioned) (%)	7.4|88.9|3.7	0|96.3|3.7	.388
Duration of pain (years) (mean ± SD)	9.9 ± 9.2	9.3 ± 8.8	.809
Pain intensity (VAS) (mean ± SD)	64.1 ± 12.8	64.4 ± 13.3	.942
Functional disability (NDI) (mean ± SD)	32.4 ± 7.2	29.3 ± 8.2	.140
Current pain medication (regularly|when needed) (%)	0|25.9	3.9|53.9	.052
Treatment history (%)			
Pain medication	48.2	70.4	.166
Injections	44.4	40.7	.783
Physical therapy	55.6	66.7	.577
Massage	74.1	77.8	.750
Acupuncture	29.6	33.3	.770
Chiropractic treatment	29.6	37.0	.773
Relaxation techniques	29.6	25.9	.761
Psychotherapy	7.4	11.1	.639
Treatment expectancy (CEQ) (mean ± SD)	7.0 ± 1.1	6.5 ± 1.4	.136

Abbreviations: CEQ: Credibility/Expectancy Questionnaire; NDI: Neck Disability Index; SD: Standard deviation; VAS: Visual Analogue Scale.

3.3 Concurrent treatments

Patients' use of concurrent pain medication is illustrated in Figure 3. During the 8 weeks of treatment, the daily intake of analgesics was 0.1 ± 0.1 DDD in the CST group and 0.5 ± 0.3 DDD in the sham group. Analysis revealed no significant main effect of time (p = .716) and group (p = .099), and no significant time-group interaction (p = .069) (see appendix). Other concurrent treatments were reported by five patients in the sham group who used massage 4 times and acupuncture 2 times.

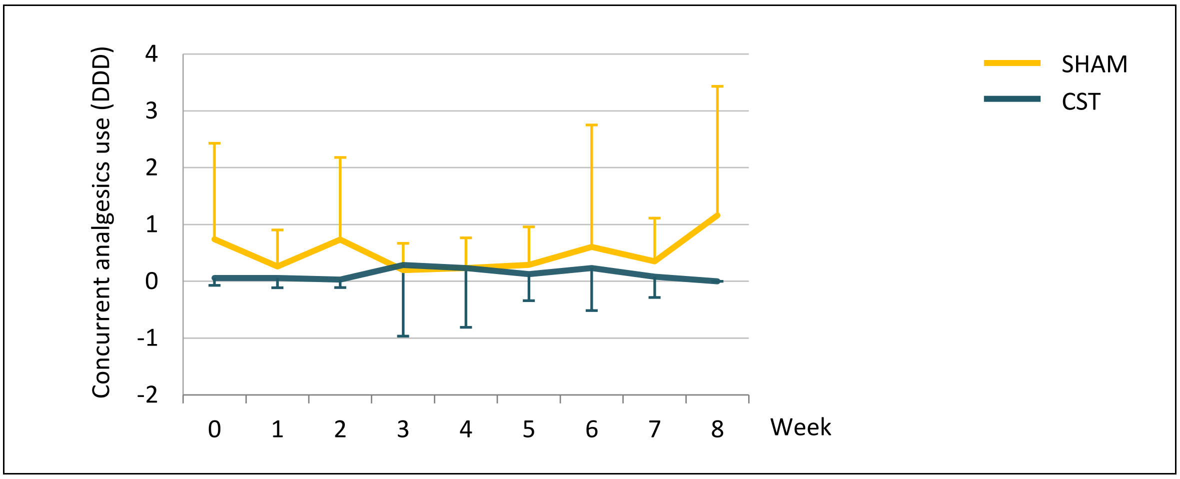

Figure 3. Concurrent analgesics use (mean ± SD) during the intervention period

3.4 Compliance with the allocated intervention

For both groups, almost similar levels of compliance were observed. Patients in the CST group attended on average 7.7 ± 0.9 of the 8 treatment units (96.3%), patients in the sham group 6.7 ± 2.4 units (83.8%). Although this group difference was not statistically significant (p = .054) (see appendix), compared to the CST group, twice as many sham patients did not attend the entire number of treatment units. Nonetheless, reasons for intermittent attendance were comparable between groups, except for three patients of the sham group who stated ineffectivity of the treatment as the reason for not attending all units provided (Figure 2).

3.5 Treatment credibility and therapeutic alliance

Results of the logistic regression modelling are shown in Table 5 and Figure 4. While the AORs of treatment expectancy, treatment consistency, treatment recommendation and alliance quality were not found to have significant predictive power (p ≥ .05) for classifying patients into the CST or sham group, treatment satisfaction revealed a significant AOR (p = .011) in the per-protocol analysis. Even so, this AOR was no longer significant in the intention-to-treat analysis (p = .060).

Table 5. Logistic regression analysis

	Predictor variable	B ± SE	P	AOR	Lower 95% CI	Upper 95% CI
Per-protocol	Treatment expectancy	0.11 ± 0.29	.701	1.12	0.64	1.96
	Treatment consistency	0.30 ± 0.25	.227	1.36	0.83	2.22
	Treatment recommendation	-0.32 ± 0.30	.281	0.73	0.40	1.30
	Alliance quality	-0.34 ± 0.51	.510	0.72	0.26	1.94
	Treatment satisfaction	1.92 ± 0.76	.011*	6.83	1.54	30.24
Intention-to-treat	Treatment expectancy	0.17 ± 0.28	.555	1.18	0.68	2.04
	Treatment consistency	0.29 ± 0.25	.253	1.33	0.82	2.18
	Treatment recommendation	-0.21 ± 0.31	.505	0.81	0.44	1.50
	Alliance quality	-0.23 ± 0.56	.687	0.80	0.26	2.41
	Treatment satisfaction	1.41 ± 0.75	.060	4.09	0.94	17.76

Abbreviations: AOR: Adjusted odds ratio; B: Beta regression coefficient; CI: Confidence interval; P: Level of significance; SE: Standard error; *: Significant influence of predictor variables (P < .05).

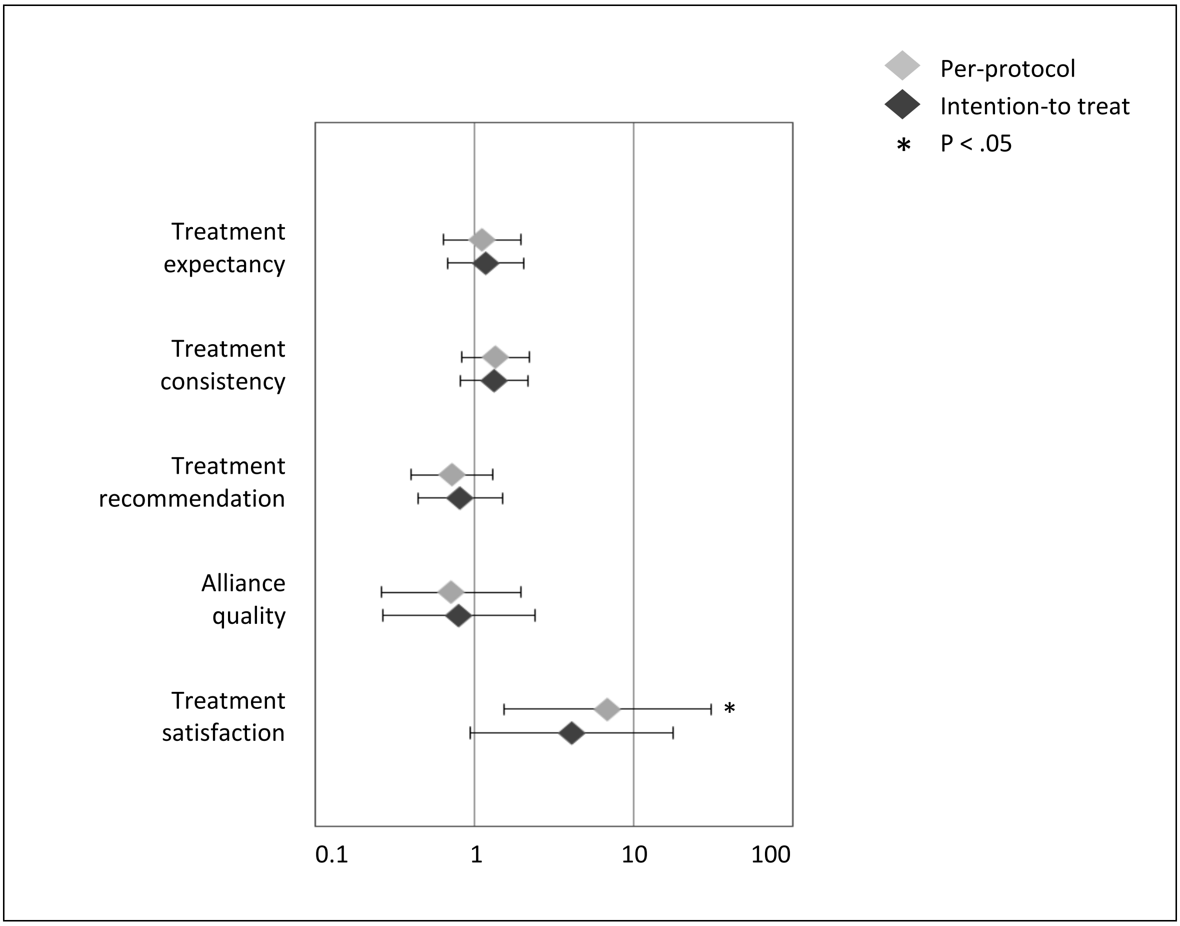

Figure 4. Predictive power (AORs ± 95% CI) of credibility and therapeutic alliance measures

3.6 Primary outcome

Effects on pain intensity are shown in Figure 5 and Table 7. In contrast to sham, patients of the CST group reported significantly less pain intensity of Δ = -21.0 mm VAS at week 8 (95% CI = [-32.6|-9.4]; p = .001; d = -1.02; 95% CI = [-1.59|-0.46]) and Δ = -16.8 mm VAS at week 20 (95% CI = [-27.5|-6.1]; p = .003; d = -0.88; 95% CI = [-1.44|-0.32]).

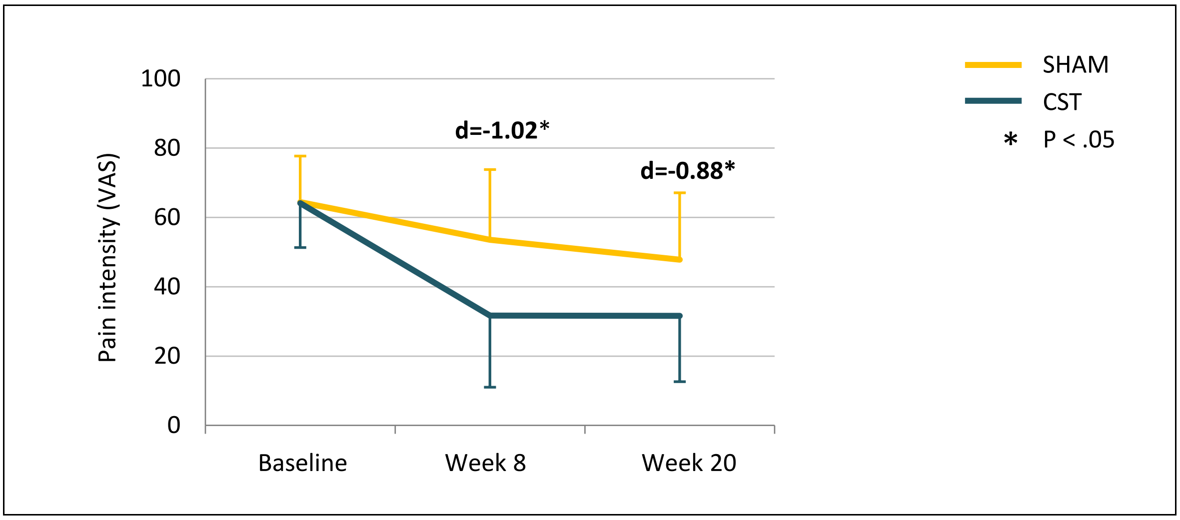

Figure 5. Effects (mean ± SD) on pain intensity

Table 6. Responder analysis of the primary outcome

	Craniosacral Therapy (n=27)		Sham (n=27)		
	Non-responder	Responder	Non-responder	Responder	P
20% VAS reduction at week 8	7 (25.9%)	20 (74.1%)	16 (59.3%)	11 (40.7%)	.013*
20% VAS reduction at week 20	6 (22.2%)	21 (77.8%)	13 (48.1%)	14 (51.9%)	.046*
50% VAS reduction at week 8	15 (55.6%)	12 (44.4%)	23 (85.2%)	4 (14.8%)	.017*
50% VAS reduction at week 20	14 (51.9%)	13 (48.1%)	20 (74.1%)	7 (25.9%)	.091

Abbreviations: P: Level of significance; *: Significant between-group difference (P < .05).

A minimal clinically important pain reduction of at least 20% was reported by 74.1% of the CST patients against 40.7% of the sham patients at week 8 (p = .013), and 77.8% of the CST patients against 51.9% of the sham patients at week 20 (p = .046). A substantial clinical benefit of at least 50% pain relief at week 8 was reported by 44.4% of the CST patients against 14.8% of the sham patients (p = .017). At week 20, a comparison of 50% response rates did not reach the level of significance (p = .091) (Table 6).

Table 7. Effects (mean ± SD) of Craniosacral Therapy in comparison with sham

		Craniosacral Therapy (n=27)			Sham (n=27)		
		Baseline	Week 8	Week 20	Baseline	Week 8	Week 20
Pain	Pain intensity (VAS)	64.1 ± 12.8	31.7 ± 20.7	31.6 ± 19.0	64.4 ± 13.3	53.5 ± 20.3	47.8 ± 19.3
	Pain on movement (POM)	54.6 ± 19.8	25.8 ± 19.5	23.4 ± 15.7	58.0 ± 17.7	46.8 ± 21.0	36.9 ± 18.9
	Point of max. pain (PPT)	234.4 ± 120.1	255.4 ± 122.9	226.5 ± 62.6	238.5 ± 137.1	206.7 ± 77.1	204.9 ± 63.4
	M. levator scapulae (PPT)	271.4 ± 109.4	290.9 ± 87.0	254.6 ± 62.8	250.5 ± 115.4	246.2 ± 85.5	241.2 ± 70.0
	M. trapezius (PPT)	241.7 ± 101.7	238.9 ± 77.6	230.4 ± 59.3	220.6 ± 108.1	200.8 ± 69.2	222.0 ± 74.3
	M. semispinalis capitis (PPT)	156.4 ± 60.1	164.2 ± 48.8	167.2 ± 58.2	162.6 ± 78.7	160.9 ± 76.5	155.6 ± 50.8
Physical health	Functional disability (NDI)	32.4 ± 7.2	17.6 ± 11.6	18.5 ± 7.5	29.3 ± 8.1	24.8 ± 10.8	23.9 ± 8.7
	Physical quality of life (SF-12)	38.0 ± 8.3	47.2 ± 9.0	48.5 ± 5.1	41.2 ± 6.0	43.3 ± 9.3	43.2 ± 5.9
	Physical well-being (FEW)	2.9 ± 0.6	3.1 ± 0.8	3.1 ± 0.6	2.7 ± 0.8	2.7 ± 0.8	2.8 ± 0.8
Mental health	Mental quality of life (SF-12)	48.5 ± 10.6	51.2 ± 9.7	48.4 ± 10.0	48.8 ± 11.4	47.7 ± 12.5	46.2 ± 12.4
	Anxiety (HADS)	7.0 ± 3.7	5.4 ± 4.3	5.1 ± 3.4	6.0 ± 3.4	5.9 ± 3.6	6.7 ± 3.8
	Depression (HADS)	4.8 ± 3.5	4.1 ± 4.0	5.0 ± 3.5	4.4 ± 3.5	4.7 ± 3.7	6.8 ± 3.8
	Stress perception (PSQ)	44.9 ± 14.6	40.8 ± 18.0	38.7 ± 15.5	47.6 ± 18.5	45.2 ± 20.3	47.2 ± 19.9
	Pain acceptance (ERDA)	2.8 ± 0.5	3.0 ± 0.7	3.2 ± 0.6	3.0 ± 0.5	3.0 ± 0.4	3.0 ± 0.5
Body awareness	Body awareness (SBC)	2.9 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	2.8 ± 0.6	2.7 ± 0.6	3.0 ± 0.5
	Body dissociation (SBC)	0.8 ± 0.4	0.8 ± 0.7	0.9 ± 0.4	0.7 ± 0.6	0.7 ± 0.5	0.8 ± 0.8
Global	Global improvement (PGI-I)	–	2.2 ± 1.0	2.3 ± 1.1	–	3.3 ± 1.0	3.1 ± 1.1

Abbreviations: CI: Confidence interval; ERDA: Emotional/Rational Disease Acceptance Questionnaire; FEW: Questionnaire for Assessing Subjective Physical Well-being; HADS: Hospital Anxiety and Depression Scale; NDI: Neck Disability Index; P: Level of significance; PGI-I: Patients' Global Impression of Improvement; POM: Pain on Movement Questionnaire; PPT: Pressure pain thresholds; PSQ: Perceived Stress Questionnaire; SBC: Scale of Body Connection; SD: Standard deviation; SF-12: 12-item Short Form Health Survey; VAS: Visual Analog Scale.

Table 7. Effects (mean ± SD) of Craniosacral Therapy in comparison to sham (continued)

		Between-group difference (95% CI)		P		Effect size (95% CI)	
		Week 8	Week 20	Week 8	Week 20	Week 8	Week 20
Pain	Pain intensity (VAS)	-21.0 [-32.6|-9.4]	-16.8 [-27.5|-6.1]	.001*	.003*	-1.02 [-1.59|-0.46]	-0.88 [-1.44|-0.32]
	Pain on movement (POM)	-18.6 [-29.2|-8.0]	-11.4 [-20.9|-1.9]	.001*	.020*	-0.92 [-1.48|-0.36]	-0.66 [-1.21|-0.11]
	Point of max. pain (PPT)	50.3 [2.8|97.7]	23.9 [-9.9|57.3]	.038*	.163	0.52 [-0.02|1.06]	0.38 [-0.16|0.91]
	M. levator scapulae (PPT)	34.2 [-2.9|71.3]	10.4 [-25.1|45.8]	.070	.560	0.40 [-0.14|0.94]	0.16 [-0.38|0.69]
	M. trapezius (PPT)	31.8 [1.2|62.4]	4.4 [-28.9|37.7]	.042*	.788	0.43 [-0.11|0.97]	0.07 [-0.47|0.60]
	M. semispinalis capitis (PPT)	5.8 [-19.2|30.8]	15.1 [-12.4|42.5]	.644	.276	0.09 [-0.44|0.62]	0.28 [-0.26|0.81]
Physical health	Functional disability (NDI)	-8.2 [-14.4|-2.1]	-6.5 [-11.1|-2.0]	.010*	.006*	-0.73 [-1.28|-0.18]	-0.80 [-1.36|-0.25]
	Physical quality of life (SF-12)	5.8 [1.3|10.4]	5.9 [2.8|9.1]	.013*	.000*	0.64 [0.09|1.18]	1.07 [0.05|1.64]
	Physical well-being (FEW)	0.2 [-0.2|0.5]	0.2 [-0.1|0.7]	.384	.155	0.19 [-0.34|0.72]	0.38 [-0.16|0.92]
Mental health	Mental quality of life (SF-12)	3.5 [-1.6|8.5]	2.7 [-3.2|8.6]	.178	.363	0.31 [-0.23|0.85]	0.24 [-0.30|0.77]
	Anxiety (HADS)	-1.0 [-2.8|0.9]	-2.1 [-3.8|-0.3]	.299	.020*	-0.24 [-0.78|0.30]	-0.58 [-1.12|-0.03]
	Depression (HADS)	-0.7 [-2.2|0.8]	-1.9 [-3.9|0.2]	.329	.079	-0.19 [-0.72|0.35]	-0.50 [-1.05|0.04]
	Stress perception (PSQ)	-0.4 [-8.2|7.4]	-6.4 [-15.5|2.8]	.912	.171	-0.02 [-0.56|0.51]	-0.36 [-0.89|0.18]
	Pain acceptance (ERDA)	0.1 [-0.2|0.4]	0.2 [-0.1|0.4]	.392	.146	0.21 [-0.33|0.74]	0.37 [-0.17|0.91]
Body awareness	Body awareness (SBC)	0.3 [0.1|0.5]	0.1 [-0.1|0.4]	.001*	.330	0.59 [0.04|1.13]	0.26 [-0.27|0.80]
	Body dissociation (SBC)	0.9 [-0.1|0.4]	0 [-0.3|0.3]	.183	.935	0.30 [-0.23|0.84]	0.02 [-0.51|0.55]
Global	Global improvement (PGI-I)	-1.0 [-1.5|-0.5]	-0.7 [-1.3|-0.1]	.000*	.029*	-1.01 [-1.58|-0.45]	-0.62 [-1.17|-0.07]

Abbreviations: CI: Confidence interval; ERDA: Emotional/Rational Disease Acceptance Questionnaire; FEW: Questionnaire for Assessing Subjective Physical Well-being; HADS: Hospital Anxiety and Depression Scale; NDI: Neck Disability Index; P: Level of significance; PGI-I: Patients' Global Impression of Improvement; POM: Pain on Movement Questionnaire; PPT: Pressure pain thresholds; PSQ: Perceived Stress Questionnaire; SBC: Scale of Body Connection; SD: Standard deviation; SF-12: 12-item Short Form Health Survey; VAS: Visual Analog Scale. *: Significant between-group difference ($P < .05$).

3.7 Secondary outcomes

Analyses of secondary outcomes are also shown in Table 7. At week 8, significant between-group differences favoring CST were detected for pain on movement ($p = .001$; $d = -0.92$) (Figure 6), pressure pain thresholds at the point of maximum pain ($p = .038$; $d = 0.52$) (Figure 7), and bilaterally at the trapezius muscle ($p = .042$; $d = 0.43$) (Figure 8), functional disability ($p = .010$; $d = -0.73$) (Figure 9), physical quality of life ($p = .013$; $d = 0.64$) (Figure 10), and body awareness ($p = .001$; $d = 0.59$) (Figure 11). At week 20, significant effects could be detected for pain on movement ($p = .020$; $d = -0.66$) (Figure 6), functional disability ($p = .006$; $d = -0.80$) (Figure 9), and physical quality of life ($p \leq .000$; $d = 1.07$) (Figure 10). Although anxiety and depression levels were reduced in the CST group and increased in the sham group, between-group comparisons were significant only for anxiety and only at week 20 ($p = .020$; $d = -0.58$) (Figure 12). No significant group differences were found for stress perception, well-being, mental quality of life, pain acceptance, and body dissociation ($p \geq 0.05$).

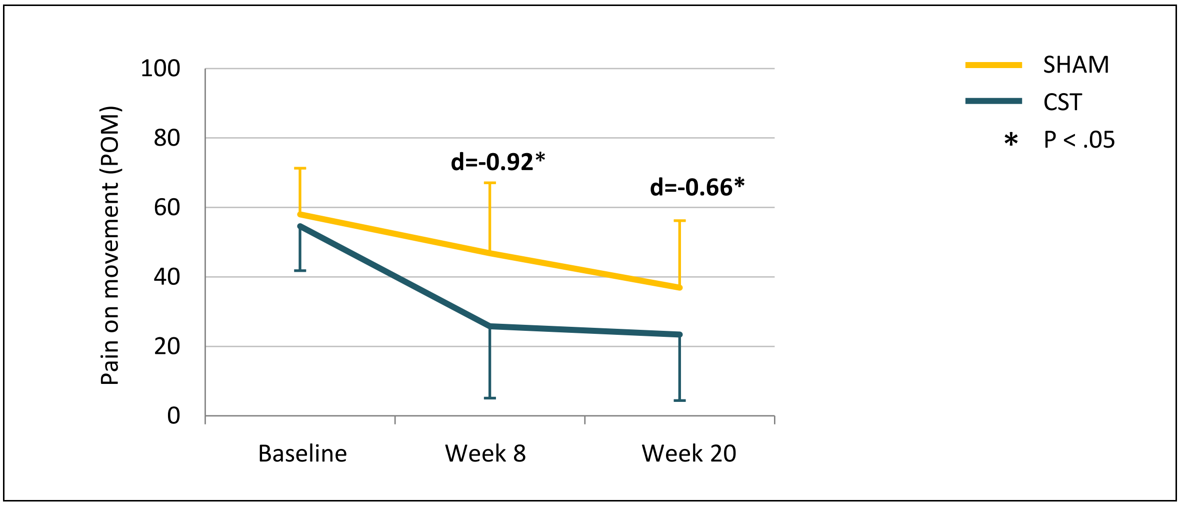

Figure 6. Effects (mean ± SD) on pain on movement

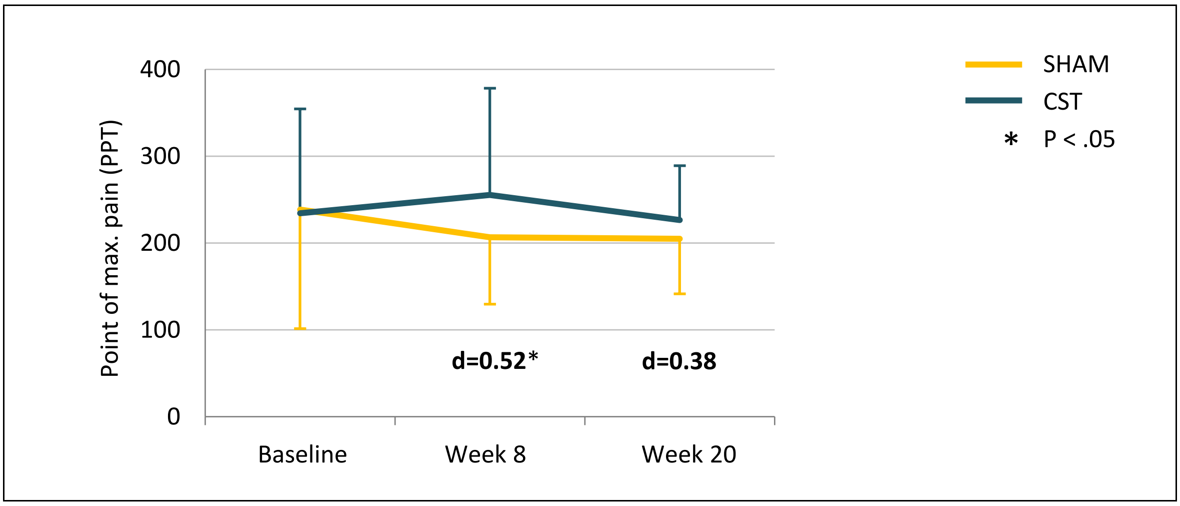

Figure 7. Effects (mean ± SD) on pressure pain thresholds at the point of maximum pain

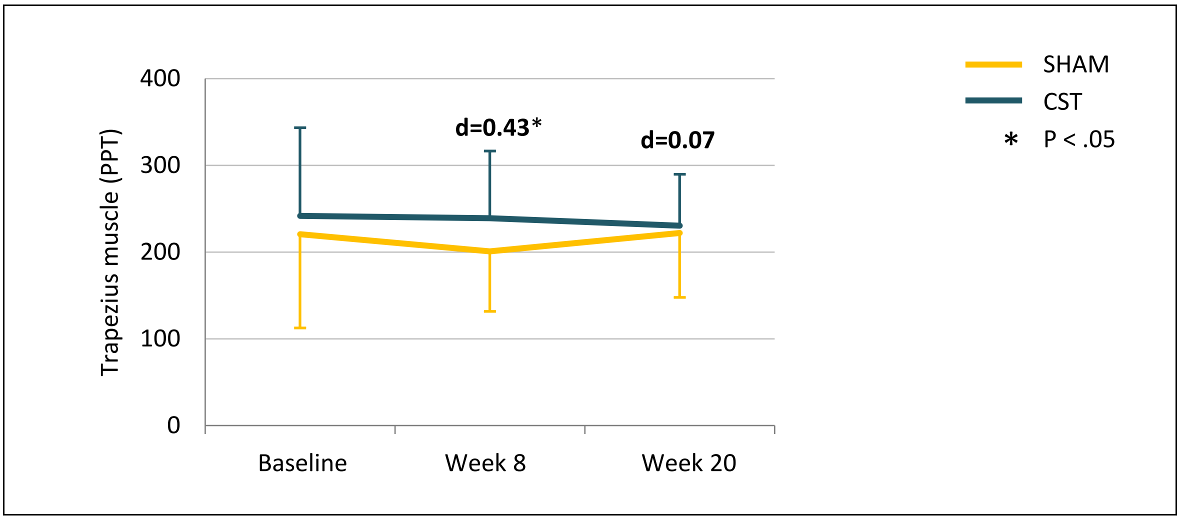

Figure 8. Effects (mean ± SD) on pressure pain thresholds bilaterally at the trapezius muscle

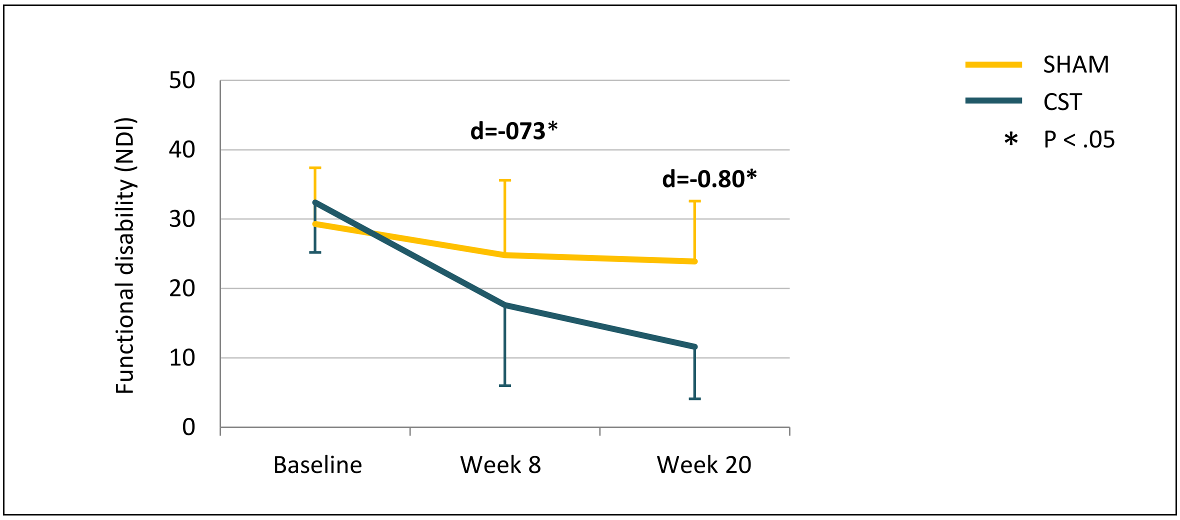

Figure 9. Effects (mean ± SD) on functional disability

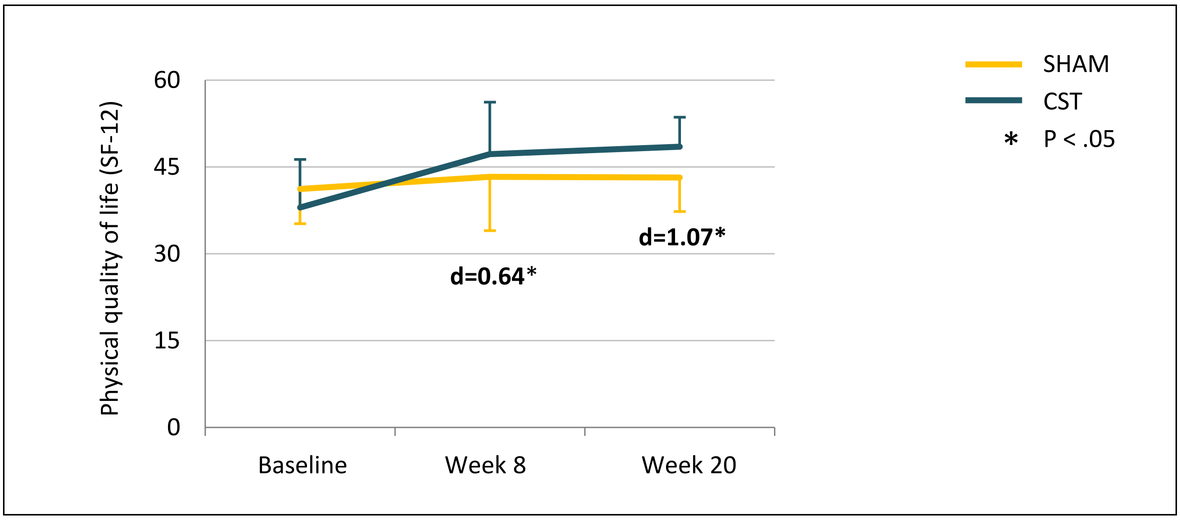

Figure 10. Effects (mean ± SD) on physical quality of life

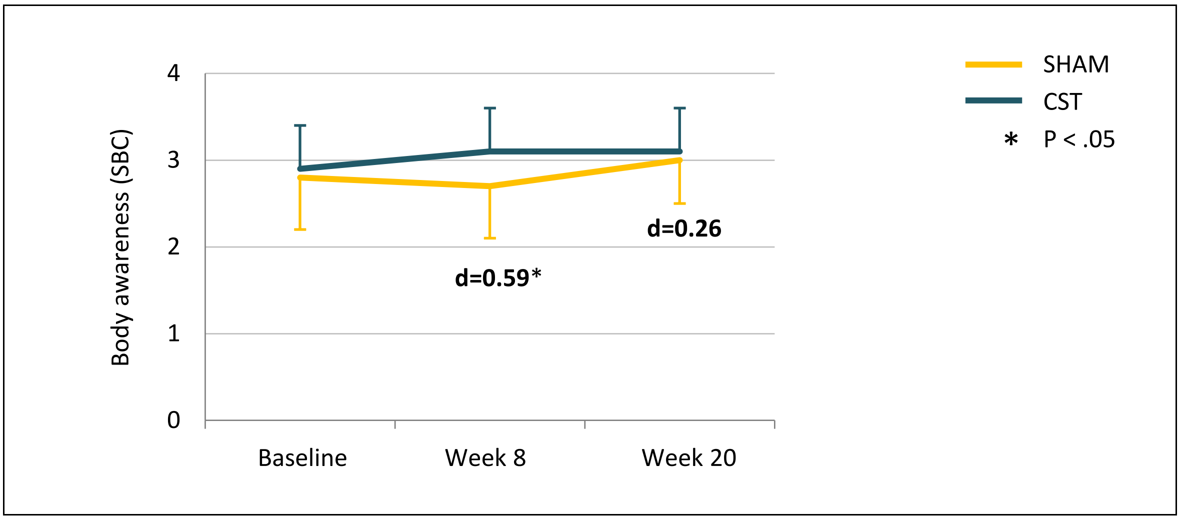

Figure 11. Effects (mean ± SD) on body awareness

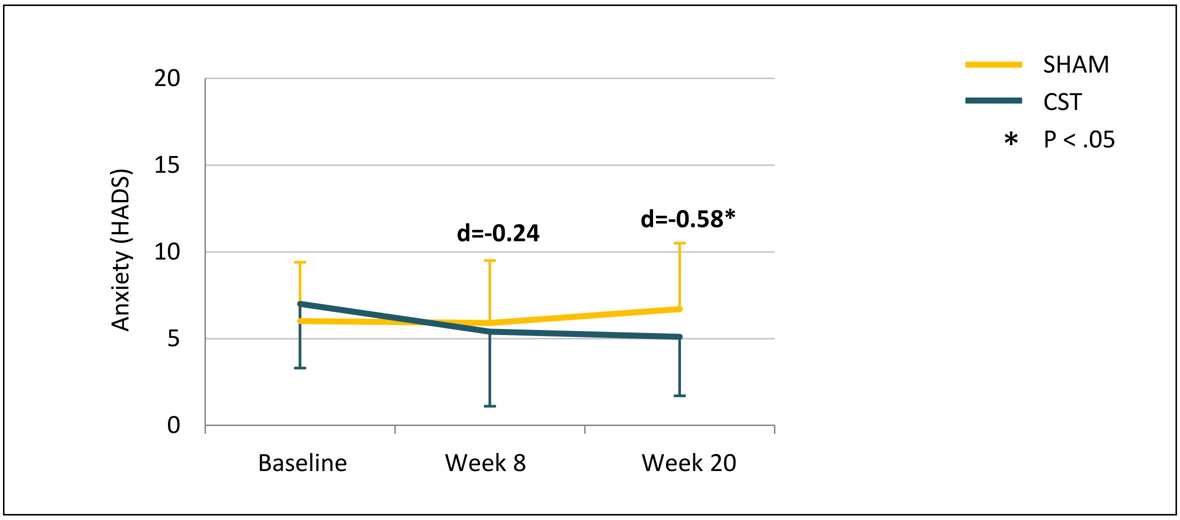

Figure 12. Effects (mean ± SD) on anxiety

3.8 Global improvement

Patients' global impression of improvement is illustrated in Figure 13. At week 8, 85.2% of the CST patients compared to 51.9% of the sham patients reported little to very much improvement. Only 14.8% of the CST patients compared to 48.1% of the sham patients reported no global change or symptom worsening. At week 20, percentages showed similar trends with 81.5% of the CST patients compared to 48.2% of the sham patients continued to report global improvement, whereas 18.5% of the CST patients against 51.8% of the sham patients still reported no change or symptom worsening compared to baseline. Differences between groups were significant for both, week 8 ($p \leq .000$; $d = -1.01$) and week 20 ratings ($p = .029$; $d = -0.62$) (Table 7).

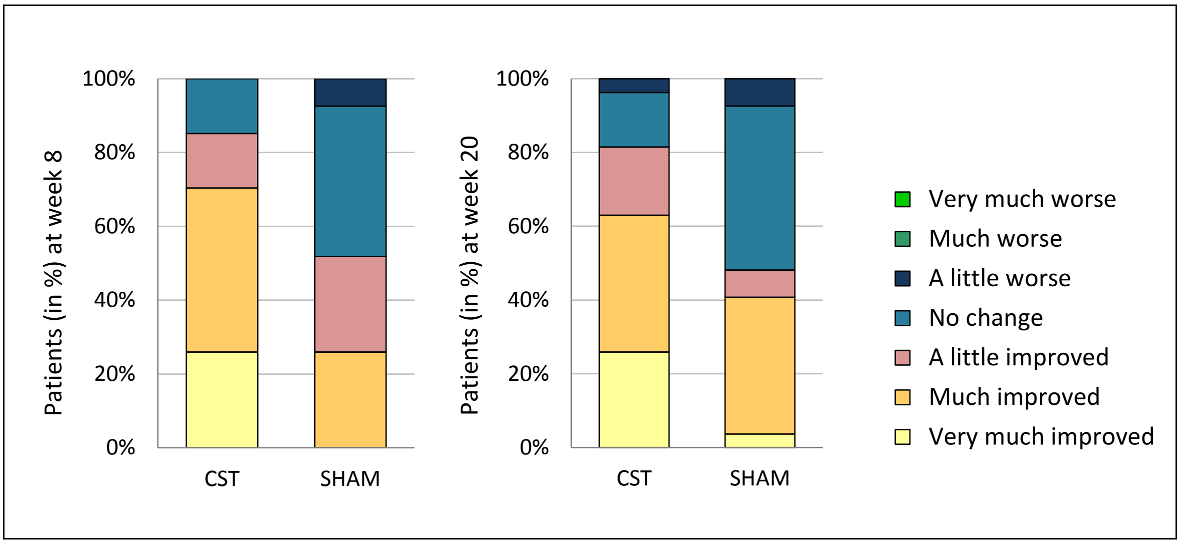

Figure 13. Effects on global improvement

3.9 Qualitative Outcomes

Results of the word frequency analysis revealed a first impression of how patients experienced the CST treatment (Figure 14). The more a term was mentioned within the 20 interviews (mean time: 21.05 ± 7.63 minutes) the larger it is displayed. With a frequency of 129, “changed” was the most mentioned term, while “change” as an active verb was stated another 16 times. Further on, patients reported that they feel “better”, “relaxed”, “pleasantly”, somehow “different” and “new” with a decreasing frequency of 112 to 24. In contrast, “worse” was mentioned only 8 times.

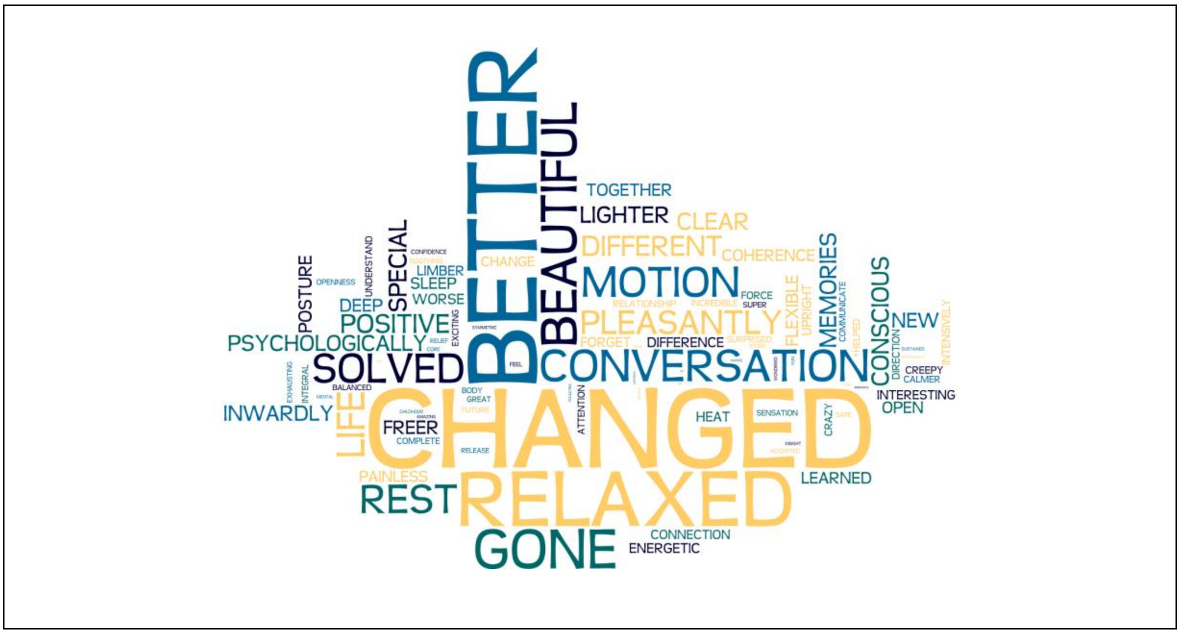

Figure 14. Word frequency analysis

The qualitative content analysis led to a deeper understanding of local and systemic physical as well as perceptual, emotional, spiritual, cognitive, behavioral and socio-economic effects of CST. Physical responses to treatment (Table 8) included reduced neck, back, and shoulder pain (Figure 15), radiated pain (Figure 16), headache and vertigo. Symptom change comprised initial aggravations, no alterations in pain and functioning, extended painless intervals, and sustained absence of pain. Patients also reported increased function and flexibility of the neck, a more upright posture and the impression of improved vision. In some patients, vagotonic activation during the therapy resulted in a continuing parasympathetic response and the experience of less physical exhaustion, which was compared with an escape from the rat race. This led to more energy and strength, increased tolerance towards stress and pain, sustained relaxation and better sleep quality.

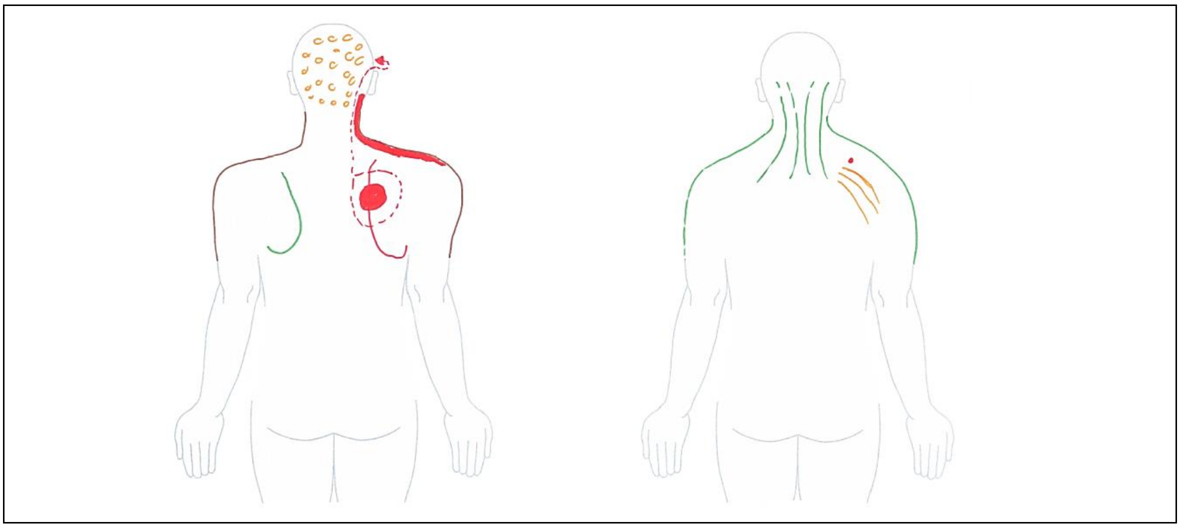

Figure 15. Body image drawing of patient 42 at baseline and week 8

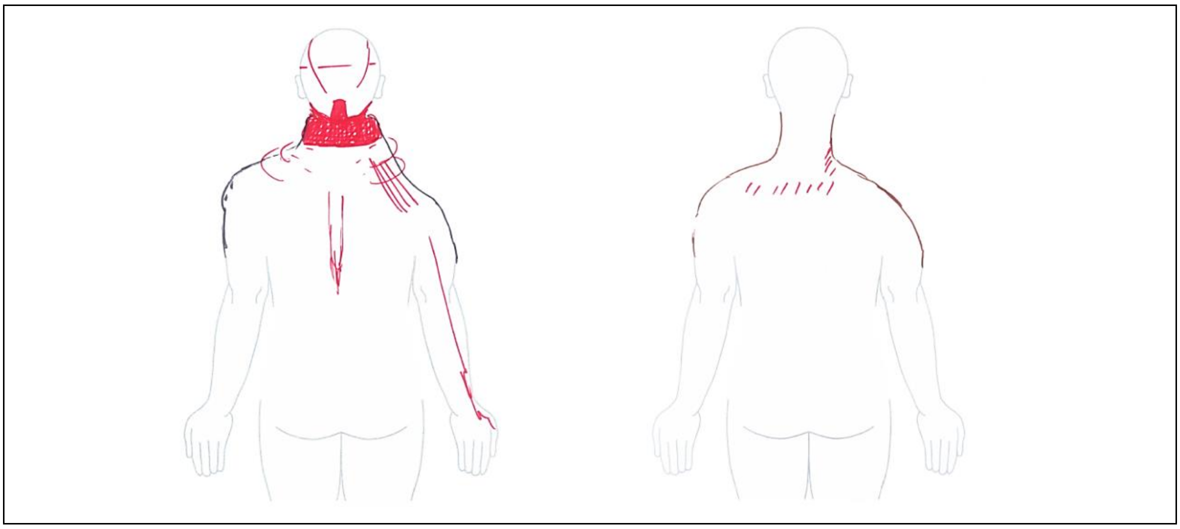

Figure 16. Body image drawing of patient 49 at baseline and week 8

Table 8. Local and systemic physical responses

Reduced symptoms	
Decreased neck and back pain	"I've drawn no more points of pain, because the neck pain is really gone. There is also no more radiated pain in the head or back." (22|8)
Less headache and vertigo	"Much less headaches and neck pain, much less. […] My dizziness is just gone, which I always had thru quick, jerky movements." (48|10,52)
No improvement	"Unfortunately, nothing has changed. […] The pain is still there." (51|8)
Increased function	
Enhanced neck function	"The neck area is softer and relaxed. As if the neck is more able to carry my head. […] The neck just more functional." (22|20)
Improved range of motion	"Because I was so tense, I had to rotate the whole body instead of the head only. This is not completely gone, but my mobility has increased enormously." (31|18)
More upright posture	"This upright feeling is remarkable. I haven't known this for many years. […] And I can keep it all day long. Thus, my position is changed, also in life." (22|8)
Sharpened senses	"I woke up the next morning and for the first time I had the feeling that I could see quite well, also without glasses." (30|38)
Autonomic responses	
Immediate vago-tonic activation	"With this deep relaxation my stomach had always bubbled." (22|26) "From head to toe, I had a warm feeling throughout the whole body." (50|22)
Parasympathetic regulation	"I can be more quickly inwards my body. I'm calmer. My nervous system activity has definitely been brought down." (14|50)
Physical recovery	
Less physical exhaustion	"I'm able to do many more things, because the pain did no longer exhaust me in such a way. I have more strength, more energy for me again." (42|14)
Escape the rat race	"All was so exhausting. […] Due to the treatment, I could pause. It was, indeed, as a complete escape from this rat race." (14|58)
Increased stress tolerance	"My stress level is higher. Today I can have more stress before my symptoms reappeared. Yes, I really can endure more stress." (42|46)
Sustained relaxation	"Even this touch, this quiet contact led to deep relaxation. […] And I was able to maintain this quietness and relaxation, also throughout the day." (13|26,36)
Better sleep quality	"I sleep better. Not necessarily more, but deeper." (35|62)

Table 9. Gain in body perception and awareness

Differentiated body perception	
Pain now locatable	"The pain has become much more defined and concrete. It is no longer such a painful, flabby, dull and vague mass. I can palpate it now." (35|50)
Less muscle tension	"It has been changing. The neck was really like a wall. And now, all is more like pleasant sand." (49|16) (Figure 16)
More fluent and vivid	"I no longer feel so restricted, all is much more fluent." (42|10) "I feel more vivid, in general" (36|34)
Sorting and unwinding of structures	"It was not massage. It was just a hold that internally has made a motion. It was so crazy, as if someone stirred. [...] I had the feeling that everything in my body is sorted and unwinded, as if all gets more space." (14|42,32)
More symmetry and balance	"I had the feeling that one shoulder was much deeper, that I had a crooked posture. […] It feels different now, as moved into the correct position." (7|10,18)
Back to normal	"I cannot assess the pain because I cannot perceive it. […] The right site simply feels pleasantly, so normal." (36|12)
Entire body image	
Reintegration of dissociated body parts	"Before the therapy, I've thought that the neck area did not really belong to me. I always felt the need to remove the head. That feeling does no longer exist." (7|20)
Increased interoceptive awareness	
Altered states of consciousness	"I could equate that [therapy] with hypnosis or trance. I was somehow promptly brought down to a state of total relaxation." (30|36)
New internal perspective	"I was able to perceive the body from a different perspective and realized that my muscles are extremely tensioned, which I was totally unaware of." (42|36)
Increased body awareness	"By hearing into my body, I've learned a lot. That was a revelation to me! […] From now on, I will look quite different at my body." (49|32,74)

Patients also reported a gain in body perception and awareness (Table 9). The area of perceived pain was reduced and more defined in contrast to the sensation of an impalpable, vague mass before CST. The feelings of tension, of being restricted within one's own body were replaced by descriptions of being more fluent and vivid. Structures got sorted, became more symmetrical and returned to a normal position. Thus, some patients reported being able to reintegrate the formerly painful, dissociated body parts into their body image. Due to the deep relaxation, patients also described states of altered consciousness enabling them to experience their bodies from a new internal perspective and to increase their interoceptive awareness.

Table 10. Emotional reprocessing

Emotional turmoil	
Initial turmoil	“That was different. There were pleasant emotions, and then I had two weeks I was standing right beside me.” (5|40)
Straining process	“That [therapy] just got down to the nitty-gritty. But no matter how hard it was; it was incredibly beneficial.” (49|56)
Emotional release	
Release of suppressed emotions	“Once, as something had released in my neck, suddenly tears were running. […] I was surprised, because I did not know such reactions from me. But it was okay. It was good. A relief.” (42|38,40)
Recollection of dissociated memories in a safe environment	“Directly the first unit was awesome. I started to tremble and got very strange memories, which were already more than 30 years ago. […] This feeling of helplessness, not being able to defend myself against that piano teacher who always humiliated me. I even smelled her again. […] But I was able to dedicate myself to this process without having fear. (49|20-26)
Emotional relief	
Integration of emotions	“During the first weeks, many things came to the surface. I cried a lot. […] But afterward, I was able to let it go and relax.” (49|18)
Relief from a burden	“That there was such a lot of undigested stored in my body. […] Today, it’s lighter. Relieved. So pleasant, no longer bearing this burden.” (5|48,26)
Elated mood	“I really was so elated after therapy. Really, as if I was a different person.” (7|10)
Increased calm	“That I became calmer, much more relaxed in dealing with my fellows.” (4|74)
Increased contentment	“My family said that I’m more satisfied, that I don’t complain about irrelevant things that often anymore.” (42|62)
Less affective pain perception	“I’ve perceived the [pain] no longer as threatening. […] Formerly, I’d always worried whether I’d have to deal with it my whole life.” (9|18)
Pointing the way to confidence	“That confidence. […] It’s not done yet but I have a compass now.” (14|60) “I face the future not as anxious as before. I think I can handle it.” (22|52)

With structural relaxation several patients reported events of emotional release (Table 10). The appearance of emotions was described as an unexpected, involuntary process, initially irritating and stirring. In some cases, suppressed emotions were related to autobiographical memories. Recollection in a setting, where patients felt safe, enabled them to reevaluate and integrate those emotions with the result of more understanding, acceptance and relief from a burden. Other patients did not experience distinct emotions during CST but expressed amazement at their elated mood, calm and contentment after treatment, which were confirmed by family and friends. Moreover, the perception of pain was described as less affective pointing the way to a new confidence with decreased anxiety about the future.

CST treatment also appeared arouse transcending experiences that were described in terms of resolution of space and time, a state of pure consciousness as well as a sense of peace, basic trust and being guarded throughout life (Table 11).

Table 11. Access to spiritual experiences

Transcending experiences	
Resolution of space and time	"It was like hovering. […] With a lot of consciousness and being continuously in the present. A resolution of space and time during therapy." (14|44,46)
Inward peace	"There was just peace in my heart." (49|34)
Sense of basic trust	"Sometimes, with the feeling of release, I had insights and the confidence that we are protected and always in good hands. Such a feeling of basic trust." (14|60)

On a cognitive level, patients perceived CST as a relief from cogitation and dysfunctional thought patterns (Table 12). During treatment, particularly the experience of a quiet mind was mentioned by some patients. This lowered mental distraction and improved overall concentration continued after therapy. On the other hand, patients reported reframing processes, whereby they experienced awareness of their own limitations and gained a new sense of self-responsibility instead of blaming the circumstances. This changed their attitude towards life and enabled patients to become more flexible in shifting their perspectives. Besides these learning processes, cognitive restructuring seemed to be associated with forgetting as well. More than one patient described difficulties to remember areas of pain and compared their impression with a hard disk that has been cleaned.

Table 12. Cognitive restructuring

Less mental distraction	
Quiet mind	"During treatment, I really had a clear mind, no inner cinema at all." (48|42)
Better concentration	"That [pain] is less. I'm so thankful. I'm more concentrated and clearer." (44|16)
Cognitive reframing	
Listen to the body's signals	"I've always thought that everything is under control, that I have no problems. But I've realized that the symptoms were signs that I ignored." (50|32)
Learning about the own limits	"It was mind-blowing, like a process of understanding how to remain in the frame. […] This responsibility, how much I can require from my body." (36|22,46)
Not to blame the circumstances	"During the treatment, I noticed that the others did not oppress me this much. I just thought that I always have to do a perfect job." (50|18)
New self-responsibility	"I get less exasperated. I feel more responsible of what I can affect and less of what I cannot." (36|52)
Seeing the other side of the coin	"These fears, how to manage family and career. I couldn't find positive aspects, although my work was all I wanted to do. But with the support of the therapist I can see it now." (22|40)
Changed attitude to life	"It's different. Before, I felt so delivered, fixed in my body. Now, it flows, even up to the head, which made me getting a different attitude towards life – it changed just from dirty brown to light blue." (49|60)
Modified pain memory	
Extinction of pain memory traces	"Sorry, I can't remember that pain on the first drawing. […] The doctor also said that there was the strongest point of pain, I didn't remember that. It is amazing that such a pain can be deleted, as a hard disk that was cleaned once." (49|14)

Behavioral changes associated with CST comprised increased self-efficacy and active coping strategies (Table 13). As a mediator for changes in coping with the pain, patients reported the interoceptive experience of body structures accompanied by increased body awareness. Thereby, they felt empowered and prepared against stress and pain. The more flexible the body was experienced, the more flexible patients became at choosing action alternatives and balancing between permission for rest and return to activity.

Table 13. Changes in coping behavior

Increased self-efficacy	
Claiming autonomy	"I got more and more of those mechanical therapies. But now I've told my doctor: 'I don't want to be manipulated anymore.' I and only I decide on my body." (31|34)
Getting empowered	"It's great that this therapy is not addictive, […] but rather the contrary. It empowers me to look more precisely on my topics." (49|80)
More active coping strategies	
Prepared against pain	"This therapy is not only relaxing but getting stronger, getting out of the wail. […] And even if I just have a little [pain], I can deal with it." (14|56,12)
Prepared against stress	"I feel somehow protected within me and I was able to distance myself better from all that stress outside. That did not reach me anymore." (14|30)
Retrieving agency	"There is just more ability to act, much more. This feeling to be flexible, not to acquiesce everything. […] I've regained control over my life." (49|28)
Permission to relax	"Just to allow myself to retreat from the daily stress, reading a good book, sitting down. I've never done this before." (42|52)
Return to activity	"I also was not able to do sports without having pain. Now I feel like I can start running again, and all is quite relaxed within me." (49|16)

Table 14. Socio-economic impact

Enhanced social quality of life	
Energy for social activities	"I'm able to accomplish things I planned, […] also positive things like outdoor activities. […] This was formerly not the case, as I always had to rest." (42|44,60)
Intensified social contacts	"I'm also able to spend more time with my friends. The contact is more intense. And this is of course great. I had restricted this part of my life so much." (42|62)
Improved work efficiency	
Working without pain	"The pulling from my neck to the forehead is much less at the moment. […] I can work efficiently again." (44|12)
Enjoying work again	"I've often ignored that [pain]. I did not want to show it. But I've no longer enjoyed my work. […] That has changed, definitely." (14|58)
Less pain medication	
Less drug intake	"When this pain gained the upper hand again, then only painkillers helped. And now my drug consumption has markedly decreased." (31|48)

Finally, patients described a decrease in their social and occupational impairment (Table 14). They experienced intensified social contacts and were able to participate in recreational activities again. Working without developing pain – even without taking drugs – led patients to enjoy their jobs again and improved work length and efficacy.

3.10 Safety

Quantitative analysis of the entire sample data resulted in no serious adverse events. Minor adverse events during or subsequent to the treatment were reported by six patients in the CST group and included: increased neck pain in two patients and complaints in the jaw area, shivering, tiredness, overwhelming emotions, and weeping in one patient, respectively. Within the sham group, eight patients reported minor adverse events that included: transient headache or migraine in seven patients, worsened neck pain in three patients, tingling sensations in two patients, and dizziness in one patient. Within both groups, symptom worsening subsided shortly after the respective treatment unit. Another two patients, one from each group, discontinued study participation because of recurrent headaches during treatment, but were free of headaches at both follow-ups.

Qualitative analysis of the CST subsample (Table 15) revealed that in particular temporary aggravation of existing symptoms and physical exhaustion after treatment were stated as minor side effects of CST. In addition, dealing with emerging emotions was reported as challenging in nearly all the patients experiencing such affects. However, for all but one patient (Table 15), emotional release was perceived as a straining and relieving process as well.

Table 15. Safety

Temporary aggravation	
Initial aggravation of symptoms	"My symptoms did not change immediately. After treatment, I even had mild aggravations. But I think that's quite normal" (31|14)
Vegetative complaints	
Physical exhaustion	"Every time after the treatment, I was tired to death. But afterwards, I was fit again." (9|28)
Emotional challenge	
Overwhelming emotional memories	"I could not allow it. That would have set off an avalanche. I felt not able to manage that emotionally. And that was okay. I have not experienced any refusal. The therapist just treated me physically. And that I could enjoy." (51|24)

4 Discussion

4.1 Summary of evidence

The present study is the first randomized controlled trial that revealed efficacy and safety of CST in comparison to manual sham treatment. In a blinded patient sample with a mean duration of 9.6 years of nonspecific neck pain, statistically significant and clinically relevant effects on pain intensity were found directly after the active treatment period as well as a further 3 months later. Minimal clinically important differences in pain intensity at week 20 were reported by almost 78% of the CST patients, whereas 48% even had substantial clinical benefit. Exploratory analyses revealed statistically significant and clinically relevant differences at week 8 and 20 for pain on movement, functional disability, physical quality of life, and patients' global impression of improvement. Pressure pain sensitivity and body awareness were significantly improved only at 8 weeks after randomization, anxiety only at week 20. No significant group differences were found for stress perception, well-being, mental quality of life, depression, pain acceptance, and body dissociation.

Qualitative analyses of patient quotes of the CST group particularly revealed changes beyond physical symptom relief. Several patients reported sustaining parasympathetic responses, which led to improved functional ability, increased tolerance towards stress and pain, and a considerably better quality of sleep. Moreover, they described an increase in interoceptive awareness, which was perceived as a significant mediator for changes in, accepting of and coping with the pain. Apart from structural alleviation, patients also reported improvements due to emotional release. Allowing for the initial turmoil, they subsequently felt relieved from suppressed feelings and dysfunctional thought patterns, thus supporting a new understanding of the pathophysiological and pathopsychological relations of pain and health. Patients who did not report distinct emotional events often also described relief in mood, contentment and confidence after treatment. For many CST patients, pain became less affective resulting in reduced anxiety and hopelessness. Other patients described their experiences during CST with words reminding them of transcending experiences during meditation. They stated feelings of basic trust and peace and moments of having a completely quiet mind. Beside cognitive silence, more than one patient reported on cognitive restructuring, not in terms of learning but of forgetting. Postulated extinction of pain memory was expressed as the difficulty to remember areas of previous pain. Behavioral changes that patients associated with CST comprised increased self-responsibility and self-efficacy. The more flexible patients experienced their physical structure, the more flexible they became in choosing action alternatives, balancing their everyday lives and returning to activity without renewed pain. Finally, patients described less social and occupational impairment with intensified family contacts and improved work joy and efficacy.

4.2 Discussion of the study results

Revealed results are in line with previous pain research on CST and recommended neck pain treatments. Where CST has been shown to be effective in improving pain syndromes in comparison to waiting list/usual care (Arnadottir & Sigurdardottir, 2013; Elden et al., 2013; Hanten et al., 1999), manual therapies (Bialoszewski et al., 2014; Castro-Sanchez et al., 2016), or non-manual sham treatments (Castro-Sanchez et al., 2011; Mataran-Penarrocha et al., 2011), this study found comparable effects in blinded patients with respect to manual sham.

Systematic reviews varied in their conclusions about CST's effectiveness. Jäkel and von Hauenschild (2012) included three randomized controlled trials on adults with fibromyalgia (Castro-Sanchez et al., 2011; Mataran-Penarrocha et al., 2011) and lateral epicondylitis (Nourbakhsh & Fearon, 2008). The authors appraised CST as effective and safe for reducing pain intensity and enhancing quality of life and sleep. However, due to overall unclear risk of selection and performance bias, conclusions remained preliminary. Another review from Ernst (2012) revealed three randomized trials of CST in adults with fibromyalgia (Castro-Sanchez et al., 2011; Mataran-Penarrocha et al., 2011) and tension-type headache (Hanten et al., 1999) and two further ones of cranial osteopathy in children with infantile colic and cerebral palsy. He considered all CST studies as having high risk of bias and concluded that CST's effectiveness was based on no more than nonspecific treatment effects. However, while Jäkel and von Hauenschild (2012) reached 8 points on the AMSTAR checklist (Shea et al., 2007) for assessing the methodological quality of systematic reviews, Ernst (2012) only got 5 of 11 accessible AMSTAR points. As Ernst (2012) is also the editor of the journal in which he published his review, his conclusions might be limited due to possible bias of the review process itself.

A more recent meta-analysis (Haller et al., 2016b) on studies on chronic pain conditions systematically searched the PubMed, CENTRAL, Scopus, PsycInfo, and CINAHL databases for CST clinical trials. This revealed nine randomized CST trials in overall 612 adults with: fibromyalgia (Castro-Sanchez et al., 2011; Mataran-Penarrocha et al., 2011), lateral epicondylitis (Nourbakhsh & Fearon, 2008), tension-type headache (Hanten et al., 1999), migraine (Arnadottir & Sigurdardottir, 2013), pelvic girdle pain (Elden et al., 2013), low back pain (Bialoszewski et al., 2014; Castro-Sanchez et al., 2016) and included the results of this study in patients with neck pain as well. Pooling the effects of CST in comparison to usual care or no treatment revealed statistically significant small to medium standardized mean differences (SMD) according to Cohen (1988) in favor of CST for pain intensity, functional disability, and physical quality of life. When compared to manual and non-manual sham treatments, effects of CST were likewise superior for pain intensity, functional disability, physical and mental quality of life and global improvement with significant SMDs ranging from small to large. In comparison to standard manipulative treatments, CST revealed significant greater SMDs of medium effect size for pain reduction and functional disability. All analyses were conducted on data assessed directly after the intervention period and were free of statistical heterogeneity indicating comparability between studies and consistency of results for short-term CST effects (Haller et al., 2016b). However, as the data pool overlaps with the earlier reviews, individual study methodology, assessed with the Cochrane risk of bias tool, was also considered as unclear in most of the trials, except for low selection bias and low attrition bias. Although more recent studies tend to be better designed and reported, the overall moderate methodological quality limits the interpretation of the results. Nevertheless, a meta-analysis of effects of placebo interventions in trials on chronic neck pain revealed only medium SMDs for short- and small SMDs for long-term placebo effects (Vernon et al., 2006). It therefore seems rather unlikely that at least some of the found CST effects on physiological as well as psychological outcomes are exclusively explainable by nonspecific treatment effects.

In comparison to recommended guideline treatments for chronic nonspecific neck pain, CST resulted in almost comparable effect sizes. When mobilization and/or manipulation plus exercise was tested against usual care, pooled effects ranged between medium SMDs for improvements in function and large SMDs for reduction of pain intensity (Gross et al., 2004). For mobilization/manipulation as a single intervention, SMDs were small to large in comparison to an inactive control treatment but did not differ from other active study treatments such as ultrasound, acupuncture, or massage (Gross et al., 2015b). For massage versus sham, meta-analyses on neck pain intensity revealed large SMDs versus inactive sham therapies but equally no significant SMDs versus other active comparators (Kong et al., 2013). Cognitive behavioral therapy was found to be significantly superior to no treatment revealing medium SMDs for pain intensity and functional disability and large SMDs for quality of life. Compared to other types of interventions, cognitive behavioral therapy did not show significant greater effects (Monticone et al., 2015). A further recommended treatment approach that revealed medium SMDs for quality of life and large SMDs for neck pain intensity, functional disability, and mood is yoga (Cramer et al., 2017), while conventional exercise revealed only small to medium SMDs (Gross et al., 2015a). In conclusion, it appears to be most effective to combine manual therapy with exercise treatments and add psychological support in cases where physiological approaches did not achieve the intended results. Complementary therapies such as yoga or CST, which already have integrated elements of mindfulness and relaxation and thus address the physical as well as mental complaints of chronic pain patients, may therefore be superior to more one-dimensional treatment concepts.

Qualitative results emphasize this conclusion. In particular, altering perceptual states during CST seems to facilitate a new level of body awareness, which in turn allows the patient to better recognize physical and mental roots of their complaints. Understanding then enables accepting and developing self-responsibility and more active coping strategies. As a result, patients gain enhanced abilities to better care for themselves and become empowered to manage their pain and life issues. Other interviewed patient samples treated with CST (Elden et al., 2014) and yoga (Cramer et al., 2013a) reported comparable mechanisms. Moreover, pain reduction, release of muscle tension and increased flexibility enable CST patients to perform sport without evoking repeated pain (Brough et al., 2014). This might be the reason why meta-analyses revealed significant higher effects for a combination of manual therapy and exercise than for exercise alone (Gross et al., 2004). In addition, patients treated with CST seem to frequently experience emotional release and relief. They particularly reported that the reconnection with their bodies led to feelings of being more secured within themselves, reduced anxiety, elated mood, and fostered confidence and a sense of peace with internal and external circumstances (Brough et al., 2014; Elden et al., 2014).

Minor adverse events during CST were comparable to previous research (Brough et al., 2014; Elden et al., 2013; Jäkel & von Hauenschild, 2012). In CST theory, transient symptom exacerbations, tiredness and emotional turmoil are usually understood as a first and sometimes sufficient response to the treatment meaning a sign of physiological regulation (Minasny, 2009; Stub et al., 2012). Each alteration of structures, regardless of whether they are physiological or mental, is associated with initial stress, which however should subside with further release of tension and symptoms (Kingston et al., 2014; Upledger & Vredevoogt, 1983). By asking patients treated with manual therapies about their assessment of vegetative or emotional side effects during or subsequent to the treatment, they rarely described them as serious or impairing adverse events (Campbell, 1999; Ekerholt & Bergland, 2006; Long & MacKay, 2003; Mazzeo, 2008; Rajendran et al., 2012).

4.3 Explanation and translation of the treatment effects

4.3.1 Effects of treating fascial tissue

Research that addresses connective tissue remodeling may explain the CST effects revealed by this study. Beside the broad nociceptive innervation of fasciae, studies have also confirmed interstitial low-threshold receptors that conduct very gentle brushstroke-like palpations via mechano-sensory Aβ afferents (Schleip, 2003). It is proposed that gently remodeling fasciae significantly alters the tone of myofibroblasts and striated muscle fibers (Schleip et al., 2010) as well as associated pain perceptions (Klingler et al., 2014). The effects of CST techniques on cranial fasciae may be explained by direct anatomical links between spinal meninges and the suboccipital musculature (Kahkeshani & Ward, 2012). Low-threshold palpation of superficial fasciae has even appeared to impact deeper visceral fasciae and the function of internal organs, which in turn may decrease tension and referred pain of cervical myotomes (Arendt-Nielsen et al., 2008; Lomba & Peper, 2013). However, fascial mechanisms have been examined mostly in vitro; in vivo studies of specific CST techniques are pending.

4.3.2 Effects of altering the autonomic nervous system response

As the perceptions of stress and pain are repeatedly associated (Linton, 2000), decreasing dorsal-vagal and sympathetic activity during and after treatment will equally contribute to sustained pain alleviation. This could be achieved by innervating fascial ruffini endings of Aβ afferents (Schleip, 2003) as well as dermal MRGPRB4 receptors of C-tactile afferents, which are exclusively activated by gentle stroking, not by noxious stimulation (Vrontou et al., 2013). In mice, pharmacogenetic activation of MRGPRB4 receptors resulted in anxiolytic effects and grooming behavior (Vrontou et al., 2013). In humans, light stroking of MRGPRB4 C-tactile afferents at a typical skin temperature showed significant higher discharge rates than cooler or warmer stroking stimuli, and was likewise perceived as positively reinforcing and pleasant (Ackerley et al., 2014). This kind of affective touch fosters social bonding (von Mohr et al., 2017) by stimulating ventral vagal activity and oxytocin secretion, which in turn reduces stress hormones and physiological arousal (Porges, 2001).

Preliminary evidence has confirmed corresponding effects of a specific CST still point technique on sympathetic nerve activity (Cutler et al., 2005) and alpha-band oscillations (Miana et al., 2013). Qualitative studies likewise suggest ventral vagal effects of CST. According to Piron's (2003) levels of relaxation, interviewed CST patients experienced simple relaxation responses accompanied by calm breathing and quietness; concentrative meditative stages characterized by mindfulness, ease, insights and serenity; as well as essential qualities of non-duality, which they described in terms of clarity, love, connectedness, self-acceptance, gratitude, and emptiness (Brough et al., 2014). As recent studies have found that deep meditation causes significantly better effects on electro-encephalography, heart rate, respiratory amplitude, and skin conductance response in contrast to usual relaxation (Tang et al., 2009), equivalent autonomic effects may be postulated for CST.

4.3.3 Effects of emotion regulation

Deep neuro-physiological relaxation may also facilitate emotional reprocessing. A systematic review of qualitative studies on manual therapies revealed nine trials on 133 heterogeneous patients treated with CST, massage, osteopathy, psychomotor physiotherapy, and shiatsu. The interviewed patients described releasing effects of suppressed emotions accompanied by muscular relaxation or induced by touch. Emotional release included expressions of fear, worry, sadness, and joy, which were in some cases related to autobiographical events (Haller et al., 2016a). A further interview study of patients treated with procaine injections found similar processing effects of initial turmoil, release and relief of emotions and symptoms, acceptance, and empowerment. In this study, the effects were associated with injections particularly in scar tissue (Haller et al., 2017). But regardless of whether emotional release is triggered by specific body postures, tissue relaxation, or affected scars, it is mostly followed by processes of integration and empowerment rather than those of dissociation and re-traumatization (Minasny, 2009). This indicates a ventral vagal activation of the parasympathetic nervous system, which is innervated by efferent fibers of the nucleus ambiguus and allows regulation of psycho-physiological processes. In contrast, when the nervous system switches to the sympathetic or dorsal vagal mode, the physiological response is either inhibition or excitation but not regulation (Porges, 2001).

Further research in patients with chronic unprocessed stress experiences confirm these observations. After those experiences, the autonomic nervous system does not return to normal ventral vagal mode but remains in a state of increased sympathetic and depressed parasympathetic activity (chronic stress response); or a state of high oscillation of both the sympathetic and dorsal-vagal system (traumatic stress response) (Payne et al., 2015). To physically process and integrate a stressful event, studies agree that cognitive exposure is often not enough. It seems to be also necessary to allow the emotional arousal and express the blocked emotions in terms of shaking, screaming or crying (Pascual-Leone & Greenberg, 2007). These motoric expressions, in turn, can contribute to a further decrease of pathological arousal, balance the autonomic tone (Gracanin et al., 2014), and facilitate new interoceptive and proprioceptive experiences of the ventral vagus mode (coherence, boding, compassion, mindfulness, etc.) that can physically correct those of the sympathetic (danger, worry, fear, anger, etc.) and dorsal vagus mode (helplessness, shame, depression, dissociation, etc.) (Payne et al., 2015; Porges, 2001). Beside involuntary muscular expressions, patients undergoing CST regularly show rapid eye movements during emotional release (Bertolucci, 2008; Upledger, 1990) – another motor consequence of mental reprocessing (Coubard, 2016) that is used therapeutically to induce sympathetic de-arousal (Sack et al., 2008) and reduce pain symptoms (Gerhardt et al., 2016).

While craniosacral elements like relaxation, imagination, or touch are not specific to CST, CST seems to stimulate specific neurophysiological pathways to limbic structures, prefrontal networks, and autonomic regulative mechanisms of the brain stem and thereby alters neurophysiological transmission of negative emotions and related somatic markers (Aybek et al., 2014; Ferguson, 2003; Miana et al., 2013; Morhenn et al., 2012; Raviv et al., 2009).

4.4 Methodological reflection

4.4.1 Trial design

To facilitate efficacy research, it is imperative to test a treatment against a valid and credible sham intervention with successful patient-blinding. Although previous studies queried the use of manual sham procedures for clinical trials of CST (Curtis et al., 2011; Elden et al., 2013), the results of the present study illustrate that the implementation of a manual sham treatment is feasible for therapists and tolerable for patients. None of the expectancy, credibility or alliance measures was found to be a significant predictor of group affiliation. Only satisfaction with the allocated treatment seemed to have certain influence, but did not show significant predictive power in the intention-to-treat analysis, which sought to adjust for systematic bias due to drop-out. The good compliance of both CST and sham patients corroborates the tolerability of the sham protocol used. Even though the attendance was 12.5% less than in the CST group, this difference did not reach the level of significance. Reasons for canceled appointments were also similar between groups, except for three sham patients, who stated that the treatment seems to be ineffective. For these cases, blinding may not have been successful. However, study results suggest that patients' overall compliance was related to other, non-systematic factors than lacking credibility of the sham protocol. While non-manual sham controls have been assessed as inappropriate for CST clinical trials (Curtis et al., 2011), the sham condition of this study is the first one that complies with the CST protocol in terms of duration, frequency, procedure and therapist attention. Moreover, it is safe and credible to patients and enables the interpretation of the study results independently from the quality of the alliance between patient and therapist. To the greatest possible extent variables such as empathy or simple touch, which are also shown to affect pain perception (Goldstein et al., 2016; So et al., 2008), can therefore be excluded as an explanation of the revealed differences between CST and sham.

4.4.2 Sample characteristics

The sample recruited for this study reported a long history of chronic neck complaints. The mean baseline intensity of 64 mm VAS indicates an initially moderate (Jensen et al., 2003) but even 18 mm higher intensity than in other trials of complementary treatments (Lauche et al., 2014a). In neck pain patients treated with physical therapies, elevated severity of baseline neck pain was identified as an independent predictor of poor study outcome. Other predictors included low educational level, low treatment expectation, and high levels of anxiety and depression (Hill et al., 2007). In this sample, two thirds of the patients had at least high school education, expectations were high as well, while levels of anxiety and depression only reached the boarder of subthreshold symptoms. Thus, the study outcomes seem to be not affected systematically by high or low baseline values. As the sample was naive with respect to CST, positive previous experiences can also be excluded as a possible source of bias of the study outcome.

Study patients reported using a great range of conventional and complementary treatments, which mostly complied with the recommended guidelines therapies (Childs et al., 2008; Cote et al., 2016; Scherer & Chenot, 2016). They most often received pain medication, physical therapy, and massage complemented with injections, acupuncture, relaxation techniques, and to a lesser extent psychotherapy. Despite this, 40% of the baseline sample still reported the need to take over-the-counter analgesics. During the 8 weeks of treatment, the daily intake of analgesics decreased in both study groups but showed considerable peaks in the sham group. The sham group also reported the use of other concurrent therapies including massage 4 times and acupuncture 2 times, while the CST group did not. It can therefore be concluded that neither previous nor concurrent treatments significantly biased the follow-up neck pain complaints.

4.4.3 Outcome measures

In addition to standard questionnaires, this trial included objective physiological measures as well as qualitative methods. The use of pressure pain stimulation should verify potential changes of primary and secondary hyperalgesia, which in turn would allow conclusions about neuro-physiological CST mechanisms. In this study, the intended increase in PPTs was achieved only at short-term at the point of maximum pain and bilateral at the trapezius muscle. This raises the question, why subjective self-report measures have found significant follow-up effects and objective physiological measures did not? However, whether or not this discrepancy can be explained by lacking CST effectiveness or lacking PPT validity cannot be answered conclusively. Although studies have shown the reliability of measuring PPTs (Johnston et al., 2008; Roldan & Abdi, 2015), PPTs also depend on variables such as patient expectations, individual attention and motor skills (Hansson et al., 2007). Moreover, a re-analysis of 346 patients with neck pain has found that PPT follow-up values only intercorrelated with their respective baseline scores but not with self-reported neck pain intensity at follow-up (Lauche et al., 2014a).

Between quantitative and qualitative outcome measures, this study found larger overlaps. Both analyses revealed changes in pain intensity, pain on movement, functional disability, and physical quality of life. For some other outcomes, quantitative and qualitative analyses revealed contrasting results. While body awareness was shown to be significantly improved only immediately after the 8 weeks of CST, patients interviewed mostly perceived sustained changes, even in those cases that did not experience improvements in pain intensity. Body dissociation did not show any changes in the quantitative analyses, but several patients reported a reintegration of dissociated body parts and a more entire body image in the qualitative analysis. Individual patients also reported that they were indeed unaware of their distorted body image before CST and therefore tended to ceiling effects when answering the baseline questionnaire. Similar variances appeared for subscales of the FEW, which did not show significant improvements in the quantitative analysis. In contrast, interview data revealed increased stress resilience, vitality, inner peace, and the ability to enjoy for several of the patients. The quantitative analyses of mental health outcomes might be underpowered to detect significant changes in a patient sample with comparably low baseline impairment. By pooling effects of multiple studies, mental quality of life was also found to be significantly improved in contrast to manual and non-manual sham (Haller et al., 2016b). Qualitative analyses also found evidence for the improvement in anxiety, depressive symptoms, stress perception and pain acceptance. On the global improvement scale, CST patients showed the largest differences in comparison to sham. However, these effects are most likely overestimated, as retrospective data tend to be vulnerable to recall biases (Blome & Augustin, 2015).

Moreover, the credibility instrument (CEQ) was used in an adapted, non-validated version and was not revalidated before the application to the current study patients. The performed component analysis admittedly did confirm the original factor structure, but was executed only post hoc. In addition, timing of the CEQ assessment could have been inadequate. Recommendations varied from the assessment before randomization, the administration after exposure of the first treatment, and end-of-trial tests (Kolahi et al., 2009). In this study, patients' expectations about their clinical improvement were obtained before randomization; credibility items post treatment at week 8 taking into account that unblinding may occur at any stage during the study period (Kolahi et al., 2009). However, the correlation of credibility ratings with treatment success might argue against the assessment after the end of the intervention (Sackett, 2004).

4.5 Strengths and weaknesses

The strengths of the study design comprise the random and concealed allocation procedure, the intention-to-treat analysis, the active attention- and touch-control condition, the comparable concurrent treatments and similar attendance rates as well as the successful blinding of patients and outcome assessors. Beside the rigorous quantitative design using objective, validated methods, the inclusion of qualitative methods emphasized the individual patient experiences during the CST treatment. This contributed much to the comprehension of the mechanisms of action as well as the domains of treatment outcome.

However, there are certain limitations. Firstly, the sample size was relatively small and consisted of 81.5% of female patients, which both may reduce the representativity and generalizability of the study results. Even so, most of the analyses had adequate statistical power, which suggests replicable effects in bigger samples. Epidemiological surveys also showed higher neck pain prevalences in women (Fejer et al., 2006; Hogg-Johnson et al., 2008) as well as a higher interest of woman in complementary therapies (Kristoffersen et al., 2014), which in turn would explain the greater participation of women compared to men. Secondly, the comparability of the CST and sham group may have been limited due to the allocation to the therapists as three therapists performed the CST treatments and one therapist the sham treatments. However, the logistic regression analysis has shown that the alliance to the assigned therapists did not systematically affect the study outcomes. Nonetheless, the treatment protocols used only allow for conclusions about the effect of CST on subjective clinical outcomes. It remains unclear whether CST techniques actually affect fascial structures and joints, and if so, whether these changes in turn would result in quantifiable physiological responses. A trial design would therefore have to include further objective physiological measures and an even more standardized application of fascial palpation techniques.

4.6 Conclusions and further perspectives

In comparison to manual sham, CST was shown to be effective and safe in reducing neck pain intensity and may improve functional disability and quality of life up to 3 months post intervention. For chronic and recurrent neck pain, CST may be a worthwhile treatment option in addition to standard medical care. CST may be most effective in patients who require a treatment approach for both physiological and mental complaints or in those who were currently unable to perform exercises. Further studies with rigorous methodological designs and long-term follow-ups are required to confirm CST efficacy in neck pain patients.

5 Summary

Chronic neck pain is a significant public health problem with several evidence-based treatment options. However, rates of recurrence are still high requiring research on additional approaches for the management of chronic and, in particular, nonspecific neck pain. As studies have revealed the frequent use of Craniosacral Therapy (CST) by patients suffering from neck complaints, this is the first study that aimed to investigate the efficacy of CST on chronic nonspecific neck pain in comparison to manual sham treatment.

According to apriori sample size calculations, 54 patients (44.6 ± 10.0 years, 81.5% female) with chronic nonspecific neck pain were randomized to either 8 weekly units of CST or light touch sham treatment. Patients were blinded to treatment allocation and were analyzed before and after the treatment (week 8) and a further 3 months later (week 20) using intention-to-treat analysis. The primary outcome was pain intensity measured on a visual analogue scale. Secondary outcomes included pain on movement, pressure pain sensitivity, functional disability, health-related quality of life, well-being, anxiety, depression, stress perception, pain acceptance, body awareness, patients' global improvement, and safety. Qualitative outcomes were assessed by semi-structured interviews.

In comparison to manual sham, CST patients reported significant and clinically relevant effects on pain intensity at week 8 (-21 mm; 95% confidence interval = [-32.6|-9.4]; p = .001; effect size = 1.02) as well as at week 20 (-16.8 mm; 95% confidence interval = [-27.5|-6.1]; p = .003; effect size = 0.88), while concurrent intake of analgesics did not significantly differ between groups. Minimal clinically important differences in pain intensity at week 20 were reported by 78% of the CST patients, while 48% even had substantial clinical benefit. Significant differences at week 8 and 20 were also found for pain on movement, functional disability, physical quality of life, and patients' global improvement. Pressure pain sensitivity and body awareness were significantly improved only at week 8, anxiety only at week 20. No serious adverse events were reported. Qualitative content analysis led to hypotheses of possible CST mechanisms on autonomic nervous system plasticity, emotional regulation, and mental reprocessing. Those may explain CST effects on pain, increased interoceptive awareness, emotional release, elevated mood and confidence, changes in self-efficiency and coping strategies, intensified social contacts and improved work efficacy.

In conclusion, CST was shown to be both specifically effective and safe in reducing neck pain intensity and may improve physiological and mental function up to 3 months post intervention. Further efficacy and comparative effectiveness studies with rigorous methodological designs and long-term follow-ups are required.

7 References

1. Ackerley, R., Backlund Wasling, H., Liljencrantz, J., Olausson, H., Johnson, R. D., Wessberg, J. (2014): Human C-tactile afferents are tuned to the temperature of a skin-stroking caress. J Neurosci. 34(8), 2879-2883.
2. Alban, M. W., Pocknell, V. (2017): Cognitive Factors Affecting Freeze-like Behavior in Humans. J Gen Psychol. 144(2), 140-156.
3. Albani, C., Blaser, G., Geyer, M., Schmutzer, G., Hinz, A., Bailer, H., Grulke, N., Brahler, E. (2006): [Validation and standardization of the "Questionnaire for Assessing Subjective Physical Well-Being" by Kolip and Schmidt in a representative German sample]. Psychother Psychosom Med Psychol. 56(3-4), 172-181.
4. Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., Glover, G. H., Gabrieli, J. D. (2004): Neural systems underlying the suppression of unwanted memories. Science. 303(5655), 232-235.
5. Arendt-Nielsen, L., Schipper, K. P., Dimcevski, G., Sumikura, H., Krarup, A. L., Giamberardino, M. A., Drewes, A. M. (2008): Viscero-somatic reflexes in referred pain areas evoked by capsaicin stimulation of the human gut. Eur J Pain. 12(5), 544-551.
6. Arnadottir, T. S., Sigurdardottir, A. K. (2013): Is craniosacral therapy effective for migraine? Tested with HIT-6 Questionnaire. Complement Ther Clin Pract. 19(1), 11-14.
7. Aybek, S., Nicholson, T. R., Zelaya, F., O'Daly, O. G., Craig, T. J., David, A. S., Kanaan, R. A. (2014): Neural correlates of recall of life events in conversion disorder. JAMA Psychiatry. 71(1), 52-60.
8. Bassler, M., Potratz, B., Krauthauser, H. (1995): [The "Helping Alliance Questionnaire" (HAQ) by Luborsky]. Psychotherapeut. 40(1), 23–32.
9. Bassols, A., Bosch, F., Banos, J. E. (2002): How does the general population treat their pain? A survey in Catalonia, Spain. J Pain Symptom Manage. 23(4), 318-328.
10. Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., Rainero, I. (2003): Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci. 23(10), 4315-4323.
11. Benjamin, M. (2009): The fascia of the limbs and back--a review. J Anat. 214(1), 1-18.
12. Bertolucci, L. F. (2008): Muscle Repositioning: a new verifiable approach to neuro-myofascial release? J Bodyw Mov Ther. 12(3), 213-224.
13. Bialosky, J. E., Bishop, M. D., George, S. Z., Robinson, M. E. (2011): Placebo response to manual therapy: something out of nothing? J Man Manip Ther. 19(1), 11-19.

14. Bialoszewski, D., Bebelski, M., Lewandowska, M., Slupik, A. (2014): Utility of craniosacral therapy in treatment of patients with non-specific low back pain. Preliminary report. Ortop Traumatol Rehabil. 16(6), 605-615.

15. Blome, C., Augustin, M. (2015): Measuring change in quality of life: bias in prospective and retrospective evaluation. Value Health. 18(1), 110-115.

16. Boos, N., Rieder, R., Schade, V., Spratt, K. F., Semmer, N., Aebi, M. (1995): The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. Spine (Phila Pa 1976). 20(24), 2613-2625.

17. Bot, S. D., van der Waal, J. M., Terwee, C. B., van der Windt, D. A., Schellevis, F. G., Bouter, L. M., Dekker, J. (2005): Incidence and prevalence of complaints of the neck and upper extremity in general practice. Ann Rheum Dis. 64(1), 118-123.

18. Brough, N., Lindenmeyer, A., Thistlethwaite, J., Lewith, G., Stewart-Brown, S. (2014): Perspectives on the effects and mechanisms of craniosacral therapy: A qualitative study of users' views. Eur J Integr Med. 7(2), 172-183.

19. Büssing, A., Matthiessen, P. F., Mundle, G. (2008): Emotional and rational disease acceptance in patients with depression and alcohol addiction. Health Qual Life Outcomes. 6, 4.

20. Campbell, A. (1999): The Limbic System and Emotion in Relation to Acupuncture. Acupunct Med. 17(2), 124-130.

21. Carroll, L. J., Hogg-Johnson, S., van der Velde, G., Haldeman, S., Holm, L. W., Carragee, E. J., Hurwitz, E. L., Cote, P., Nordin, M., Peloso, P. M., Guzman, J., Cassidy, J. D. (2009): Course and prognostic factors for neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. J Manipulative Physiol Ther. 32(2 Suppl), S87-96.

22. Castro-Sanchez, A. M., Lara-Palomo, I. C., Mataran-Penarrocha, G. A., Saavedra-Hernandez, M., Perez-Marmol, J. M., Aguilar-Ferrandiz, M. E. (2016): Benefits of Craniosacral Therapy in Patients with Chronic Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 22(8), 650-657.

23. Castro-Sanchez, A. M., Mataran-Penarrocha, G. A., Sanchez-Labraca, N., Quesada-Rubio, J. M., Granero-Molina, J., Moreno-Lorenzo, C. (2011): A randomized controlled trial investigating the effects of craniosacral therapy on pain and heart rate variability in fibromyalgia patients. Clin Rehabil. 25(1), 25-35.

24. Chaudhry, H., Huang, C.-Y., Schleip, R., Ji, Z., Bukiet, B., Findley, T. (2007): Viscoelastic behavior of human fasciae under extension in manual therapy. J Bodyw Mov Ther. 11(2), 159-167.

25. Childs, J. D., Cleland, J. A., Elliott, J. M., Teyhen, D. S., Wainner, R. S., Whitman, J. M., Sopky, B. J., Godges, J. J., Flynn, T. W. (2008): Neck pain: Clinical practice guidelines linked to the International Classification of Functioning, Disability, and Health from the Orthopedic Section of the American Physical Therapy Association. J Orthop Sports Phys Ther. 38(9), A1-A34.

26. Chou, R., Peterson, K., Helfand, M. (2004): Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 28(2), 140-175.

27. Clarke, T. C., Nahin, R. L., Barnes, P. M., Stussman, B. J. (2016): Use of Complementary Health Approaches for Musculoskeletal Pain Disorders Among Adults: United States, 2012. Natl Health Stat Report(98), 1-12.

28. Cohen, J. . (1988): Statistical Power Analysis for the Behavioral Sciences. Hillsdale: Lawrence Erlbaum Associates.

29. Cote, P., van der Velde, G., Cassidy, J. D., Carroll, L. J., Hogg-Johnson, S., Holm, L. W., Carragee, E. J., Haldeman, S., Nordin, M., Hurwitz, E. L., Guzman, J., Peloso, P. M. (2008): The burden and determinants of neck pain in workers: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 33(4 Suppl), S60-74.

30. Cote, P., Wong, J. J., Sutton, D., Shearer, H. M., Mior, S., Randhawa, K., Ameis, A., Carroll, L. J., Nordin, M., Yu, H., Lindsay, G. M., Southerst, D., Varatharajan, S., Jacobs, C., Stupar, M., Taylor-Vaisey, A., van der Velde, G., Gross, D. P., Brison, R. J., Paulden, M., Ammendolia, C., David Cassidy, J., Loisel, P., Marshall, S., Bohay, R. N., Stapleton, J., Lacerte, M., Krahn, M., Salhany, R. (2016): Management of neck pain and associated disorders: A clinical practice guideline from the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J. 25(7), 2000-2022.

31. Coubard, O. A. (2016): An Integrative Model for the Neural Mechanism of Eye Movement Desensitization and Reprocessing (EMDR). Front Behav Neurosci. 10(52).

32. Cramer, H., Klose, P., Brinkhaus, B., Michalsen, A., Dobos, G. (2017): Effects of yoga on chronic neck pain: a systematic review and meta-analysis. Clin Rehabil, Epub.

33. Cramer, H., Lauche, R., Haller, H., Langhorst, J., Dobos, G., Berger, B. (2013a): "I'm more in balance": a qualitative study of yoga for patients with chronic neck pain. J Altern Complement Med. 19(6), 536-542.
34. Cramer, H., Lauche, R., Hohmann, C., Langhorst, J., Dobos, G. (2013b): Yoga for chronic neck pain: a 12-month follow-up. Pain Med. 14(4), 541-548.
35. Cramer, H., Lauche, R., Hohmann, C., Ludtke, R., Haller, H., Michalsen, A., Langhorst, J., Dobos, G. (2013c): Randomized-controlled trial comparing yoga and home-based exercise for chronic neck pain. Clin J Pain. 29(3), 216-223.
36. Cramer, H., Lauche, R., Langhorst, J., Dobos, G. J., Michalsen, A. (2014): Validation of the German version of the Neck Disability Index (NDI). BMC Musculoskelet Disord. 15(1), 91.
37. Croft, P. R., Lewis, M., Papageorgiou, A. C., Thomas, E., Jayson, M. I., Macfarlane, G. J., Silman, A. J. (2001): Risk factors for neck pain: a longitudinal study in the general population. Pain. 93(3), 317-325.
38. Curtis, P., Gaylord, S. A., Park, J., Faurot, K. R., Coble, R., Suchindran, C., Coeytaux, R. R., Wilkinson, L., Mann, J. D. (2011): Credibility of low-strength static magnet therapy as an attention control intervention for a randomized controlled study of CranioSacral therapy for migraine headaches. J Altern Complement Med. 17(8), 711-721.
39. Cutler, M. J., Holland, B. S., Stupski, B. A., Gamber, R. G., Smith, M. L. (2005): Cranial manipulation can alter sleep latency and sympathetic nerve activity in humans: a pilot study. J Altern Complement Med. 11(1), 103-108.
40. Damasio, A. R. (1996): The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci. 351(1346), 1413-1420.
41. Depue, B. E., Curran, T., Banich, M. T. (2007): Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. Science. 317(5835), 215-219.
42. Devilly, G. J., Borkovec, T. D. (2000): Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry. 31(2), 73-86.
43. Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Kerns, R. D., Ader, D. N., Brandenburg, N., Burke, L. B., Cella, D., Chandler, J., Cowan, P., Dimitrova, R., Dionne, R., Hertz, S., Jadad, A. R., Katz, N. P., Kehlet, H., Kramer, L. D., Manning, D. C., McCormick, C., McDermott, M. P., McQuay, H. J., Patel, S., Porter, L., Quessy, S., Rappaport, B. A., Rauschkolb, C., Revicki, D. A., Rothman, M., Schmader, K. E., Stacey, B. R., Stauffer, J. W., von Stein, T., White, R. E., Witter, J., Zavisic, S. (2008): Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 9(2), 105-121.

44. Eisenberger, N. I. (2012): The neural bases of social pain: evidence for shared representations with physical pain. Psychosom Med. 74(2), 126-135.

45. Ekerholt, K., Bergland, A. (2006): Massage as interaction and a source of information. Eur J Physiother. 8(3), 137-144.

46. Elden, H., Lundgren, I., Robertson, E. (2014): Effects of craniosacral therapy as experienced by pregnant women with severe pelvic girdle pain: An interview study. Clin Nursing Stud. 2(3), 140-151.

47. Elden, H., Ostgaard, H. C., Glantz, A., Marciniak, P., Linner, A. C., Olsen, M. F. (2013): Effects of craniosacral therapy as adjunct to standard treatment for pelvic girdle pain in pregnant women: a multicenter, single blind, randomized controlled trial. Acta Obstet Gynecol Scand. 92(7), 775-782.

48. Engel, G. L. (1977): The need for a new medical model: a challenge for biomedicine. Science. 196(4286), 129-136.

49. Ernst, E. (2012): Craniosacral therapy: a systematic review of the clinical evidence. Focus Altern Complement Ther. 17(4), 197-201.

50. Ernst, E., Harkness, E. (2001): Spinal manipulation: a systematic review of sham-controlled, double-blind, randomized clinical trials. J Pain Symptom Manage. 22(4), 879-889.

51. European Medicines Agency. (2002): ICH Harmonised Tripartite Guideline E6 (R1). Step 5. Note For Guidance on Good Clinical Practice (CPMP/ICH/135/95). London: European Medicines Agency.

52. Feise, R. J. (2002): Do multiple outcome measures require p-value adjustment? BMC Med Res Methodol. 2, 8.

53. Fejer, R., Kyvik, K. O., Hartvigsen, J. (2006): The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J. 15(6), 834-848.

54. Ferguson, A. (2003): A review of the physiology of cranial osteopathy. J Osteopath Med. 6(2), 74-84.

55. Fliege, H., Rose, M., Arck, P., Walter, O. B., Kocalevent, R. D., Weber, C., Klapp, B. F. (2005): The Perceived Stress Questionnaire (PSQ) reconsidered: validation and reference values from different clinical and healthy adult samples. Psychosom Med. 67(1), 78-88.

56. Furlan, A. D., Yazdi, F., Tsertsvadze, A., Gross, A., Van Tulder, M., Santaguida, L., Gagnier, J., Ammendolia, C., Dryden, T., Doucette, S., Skidmore, B., Daniel, R., Ostermann, T., Tsouros, S. (2012): A systematic review and meta-analysis of efficacy, cost-effectiveness,

and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med. 2012, 953139.

57. Gage, H., Storey, L., McDowell, C., Maguire, G., Williams, P., Faithfull, S., Thomas, H., Poole, K. (2009): Integrated care: utilisation of complementary and alternative medicine within a conventional cancer treatment centre. Complement Ther Med. 17(2), 84-91.

58. Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., Turk, D. C. (2007): The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 133(4), 581-624.

59. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. (2016): Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 388(10053), 1545-1602.

60. Gerhardt, A., Leisner, S., Hartmann, M., Janke, S., Seidler, G. H., Eich, W., Tesarz, J. (2016): Eye Movement Desensitization and Reprocessing vs. Treatment-as-Usual for Non-Specific Chronic Back Pain Patients with Psychological Trauma: A Randomized Controlled Pilot Study. Front Psychiatry. 7(201).

61. Gibbs, L., Kealy, M., Willis, K., Green, J., Welch, N., Daly, J. (2007): What have sampling and data collection got to do with good qualitative research? Aust N Z J Public Health. 31(6), 540-544.

62. Goldstein, Morgenstern, H., Hurwitz, E. L., Yu, F. (2002): The impact of treatment confidence on pain and related disability among patients with low-back pain: results from the University of California, Los Angeles, low-back pain study. Spine J. 2(6), 391-399; discussion 399-401.

63. Goldstein, P., Shamay-Tsoory, S. G., Yellinek, S., Weissman-Fogel, I. (2016): Empathy Predicts an Experimental Pain Reduction During Touch. J Pain. 17(10), 1049-1057.

64. Gracanin, A., Bylsma, L. M., Vingerhoets, A. J. (2014): Is crying a self-soothing behavior? Front Psychol. 5(502).

65. Green, C., Martin, C. W., Bassett, K., Kazanjian, A. (1999). *A Systematic Review and Critical Appraisal of the Scientific Evidence on Craniosacral Therapy* Retrieved from http://faculty.une.edu/com/jnorton/BCOHTAassessment.pdf

66. Gross, A. R, Forget, M., St George, K., Fraser, M. M. H., Graham, N., Perry, L., Burnie, S., J., Goldsmith, C. H., Haines, T., Brunarski, D. (2012): Patient education for neck pain. Cochrane Database Syst Rev. (3), CD005106.

67. Gross, A. R., Hoving, J. L., Haines, T. A., Goldsmith, C. H., Kay, T., Aker, P., Bronfort, G. (2004): A Cochrane review of manipulation and mobilization for mechanical neck disorders. Spine (Phila Pa 1976). 29(14), 1541-1548.

68. Gross, A. R., Kay, T. M., Paquin, J.-P., Blanchette, S., Lalonde, P., Christie, T., Dupont, G., Graham, N., Burnie, S. J., Gelley, G., Goldsmith, C. H., Forget, M., Hoving, J., L., Brønfort, G., Santaguida, P. L. (2015a): Exercises for mechanical neck disorders. Cochrane Database Syst Rev. (1), CD004250.

69. Gross, A. R., Langevin, P., Burnie, S. J., Bédard-Brochu, M.-S., Empey, B., Dugas, E., Faber-Dobrescu, M., Andres, C., Graham, N., Goldsmith, C. H., Brønfort, G., Hoving, J. L., LeBlanc, F. (2015b): Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. Cochrane Database Syst Rev. (9), CD004249.

70. Guendel, H., O'Connor, M. F., Littrell, L., Fort, C., Lane, R. D. (2003): Functional neuroanatomy of grief: an FMRI study. Am J Psychiatry. 160(11), 1946-1953.

71. Guy, W. (1976): Clinical Global Impressions. In: W. Guy (Ed.), ECDEU Assessment Manual for Psychopharmacology, revised (pp. 217-222). Rockville: US Department of Heath, Education, and Welfare. Public Health Service. Alcohol, Drug Abuse, and Mental Health Administration.

72. Guzman, J., Hurwitz, E. L., Carroll, L. J., Haldeman, S., Cote, P., Carragee, E. J., Peloso, P. M., van der Velde, G., Holm, L. W., Hogg-Johnson, S., Nordin, M., Cassidy, J. D. (2008): A new conceptual model of neck pain: linking onset, course, and care: the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 33(4 Suppl), 14-23.

73. Haldeman, S., Carroll, L. J., Cassidy, J. D. (2008): The empowerment of people with neck pain: introduction: the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 33(4 Suppl), S8-S13.

74. Haller, H., Baumann, N., Lauche, R., Dobos, G., Ostermann, T. (2016a): Emotional release in manual therapies: a systematic review and meta-synthesis. J Altern Complement Med. 22(6), A60-61.

75. Haller, H., Cramer, H., Sundberg, T., Lauche, R., Dobos, G. (2016b): Craniosacral Therapy for Chronic Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Altern Complement Med. 22(6), A12.

76. Haller, H., Saha, F. J., Kowoll, A., Ebner, B., Berger, B., Dobos, G., Choi, K. E. (2017): Physical and emotional release effects of neural therapy: A qualitative analysis of

therapeutic mechanisms and health outcomes. BMC Complement Altern Med. 17(Suppl. 1), 94.

77. Halma, K. D., Degenhardt, B. F., Snider, K. T., Johnson, J. C., Flaim, M. S., Bradshaw, D. (2008): Intraobserver reliability of cranial strain patterns as evaluated by osteopathic physicians: a pilot study. J Am Osteopath Assoc. 108(9), 493-502.

78. Hansson, P., Backonja, M., Bouhassira, D. (2007): Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain. 129(3), 256-259.

79. Hanten, W. P., Dawson, D. D., Iwata, M., Seiden, M., Whitten, F. G., Zink, T. (1998): Craniosacral rhythm: reliability and relationships with cardiac and respiratory rates. J Orthop Sports Phys Ther. 27(3), 213-218.

80. Hanten, W. P., Olson, S. L., Hodson, J. L., Imler, V. L., Knab, V. M., Magee, J. L. (1999): The effectiveness of CV-4 and resting position techniques on subjects with tension-type headaches. J Man Manip Ther. 7(2), 64-70.

81. Harrison, R. E., Page, J. S. (2011): Multipractitioner Upledger CranioSacral Therapy: descriptive outcome study 2007-2008. J Altern Complement Med. 17(1), 13-17.

82. Hasenbring, M. I., Chehadi, O., Titze, C., Kreddig, N. (2014): Fear and anxiety in the transition from acute to chronic pain: there is evidence for endurance besides avoidance. Pain Manag. 4(5), 363-374.

83. Hasenbring, M. I., Lundberg, M., Parker, R., Soderlund, A., Bolton, B., Smeets, R. J., Ljutov, A., Simmonds, M. J. (2015): Pain, mind, and movement in musculoskeletal pain: is physical activity always health-promoting or are there detrimental aspects? Clin J Pain. 31(2), 95-96.

84. Hasenbring, M. I., Verbunt, J. A. (2010): Fear-avoidance and endurance-related responses to pain: new models of behavior and their consequences for clinical practice. Clin J Pain. 26(9), 747-753.

85. Hawk, C., Long, C. R., Rowell, R. M., Gudavalli, M. R., Jedlicka, J. (2005): A randomized trial investigating a chiropractic manual placebo: a novel design using standardized forces in the delivery of active and control treatments. J Altern Complement Med. 11(1), 109-117.

86. Henke, C., Beissner, F. (2011): [Illustrations of visceral referred pain. "Head-less" Head's zones]. Schmerz. 25(2), 132-136, 138-139.

87. Herrmann, C. (1997): International experiences with the Hospital Anxiety and Depression Scale – a review of validation data and clinical results. J Psychosom Res. 42(1), 17-41.

88. Hill, J., Lewis, M., Papageorgiou, A. C., Dziedzic, K., Croft, P. (2004): Predicting persistent neck pain: a 1-year follow-up of a population cohort. Spine (Phila Pa 1976). 29(15), 1648-1654.

89. Hill, J., Lewis, M., Sim, J., Hay, E. M., Dziedzic, K. (2007): Predictors of poor outcome in patients with neck pain treated by physical therapy. Clin J Pain. 23(8), 683-690.

90. Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., Fainsinger, R., Aass, N., Kaasa, S. (2011): Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 41(6), 1073-1093.

91. Hogg-Johnson, S., van der Velde, G., Carroll, L. J., Holm, L. W., Cassidy, J. D., Guzman, J., Cote, P., Haldeman, S., Ammendolia, C., Carragee, E., Hurwitz, E., Nordin, M., Peloso, P. (2008): The burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 33(4 Suppl), S39-51.

92. Hoy, D., March, L., Woolf, A., Blyth, F., Brooks, P., Smith, E., Vos, T., Barendregt, J., Blore, J., Murray, C., Burstein, R., Buchbinder, R. (2014): The global burden of neck pain: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 73(7), 1309-1315.

93. Hoy, D., Protani, M., De, R., Buchbinder, R. (2010): The epidemiology of neck pain. Best Pract Res Clin Rheumatol. 24(6), 783-792.

94. Hrobjartsson, A., Gotzsche, P. C. (2010): Placebo interventions for all clinical conditions. Cochrane Database Syst Rev(1), CD003974.

95. Hudson, J. I., Arnold, L. M., Bradley, L. A., Choy, E. H., Mease, P. J., Wang, F., Ahl, J., Wohlreich, M. M. (2009): What makes patients with fibromyalgia feel better? Correlations between Patient Global Impression of Improvement and changes in clinical symptoms and function: a pooled analysis of 4 randomized placebo-controlled trials of duloxetine. J Rheumatol. 36(11), 2517-2522.

96. Hughes, C. M., Quinn, F., Baxter, G. D. (2011): Complementary and alternative medicine: Perception and use by physiotherapists in the management of low back pain. Complementary Therapies in Medicine. 19(3), 149-154.

97. Hurvitz, E. A., Leonard, C., Ayyangar, R., Nelson, V. S. (2003): Complementary and alternative medicine use in families of children with cerebral palsy. Dev Med Child Neurol. 45(6), 364-370.

98. Hurwitz, E. L., Carragee, E. J., van der Velde, G., Carroll, L. J., Nordin, M., Guzman, J., Peloso, P. M., Holm, L. W., Cote, P., Hogg-Johnson, S., Cassidy, J. D., Haldeman, S. (2008): Treatment of neck pain: noninvasive interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 33(4 Suppl), S123-152.

99. Jäkel, A., von Hauenschild, P. (2012): A systematic review to evaluate the clinical benefits of craniosacral therapy. Complement Ther Med. 20(6), 456-465.

100. Jeitler, M., Brunnhuber, S., Meier, L., Ludtke, R., Bussing, A., Kessler, C., Michalsen, A. (2015): Effectiveness of jyoti meditation for patients with chronic neck pain and psychological distress--a randomized controlled clinical trial. J Pain. 16(1), 77-86.

101. Jenkinson, C., Layte, R., Jenkinson, D., Lawrence, K., Petersen, S., Paice, C., Stradling, J. (1997): A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? J Public Health Med. 19(2), 179-186.

102. Jensen, M. P., Chen, C., Brugger, A. M. (2003): Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 4(7), 407-414.

103. Johnston, V., Jimmieson, N. L., Jull, G., Souvlis, T. (2008): Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. Pain. 137(2), 257-265.

104. Jun, D., Zoe, M., Johnston, V., O'Leary, S. (2017): Physical risk factors for developing non-specific neck pain in office workers: a systematic review and meta-analysis. Int Arch Occup Environ Health. 21(10), 017-1205.

105. Kahkeshani, K., Ward, P. J. (2012): Connection between the spinal dura mater and suboccipital musculature: evidence for the myodural bridge and a route for its dissection--a review. Clin Anat. 25(4), 415-422.

106. Kalauokalani, D., Cherkin, D. C., Sherman, K. J., Koepsell, T. D., Deyo, R. A. (2001): Lessons from a trial of acupuncture and massage for low back pain: patient expectations and treatment effects. Spine (Phila Pa 1976). 26(13), 1418-1424.

107. Keay, K. A., Li, Q. F., Bandler, R. (2000): Muscle pain activates a direct projection from ventrolateral periaqueductal gray to rostral ventrolateral medulla in rats. Neurosci Lett. 290(3), 157-160.

108. Keefe, F. J., Rumble, M. E., Scipio, C. D., Giordano, L. A., Perri, L. M. (2004): Psychological aspects of persistent pain: current state of the science. J Pain. 5(4), 195-211.

109. Kingston, L., Claydon, L., Tumilty, S. (2014): The effects of spinal mobilizations on the sympathetic nervous system: a systematic review. Man Ther. 19(4), 281-287.

110. Kjaer, P., Kongsted, A., Hartvigsen, J., Isenberg-Jorgensen, A., Schiottz-Christensen, B., Soborg, B., Krog, C., Moller, C. M., Halling, C. M. B., Lauridsen, H. H., Hansen, I. R., Norregaard, J., Jorgensen, K. J., Hansen, L. V., Jakobsen, M., Jensen, M. B., Melbye, M., Duel, P., Christensen, S. W., Povlsen, T. M. (2017): National clinical guidelines for non-surgical treatment of patients with recent onset neck pain or cervical radiculopathy. Eur Spine J. 18(10), 017-5121.

111. Klein, R., Bareis, A., Schneider, A., Linde, K. (2013): Strain-counterstrain to treat restrictions of the mobility of the cervical spine in patients with neck pain: a sham-controlled randomized trial. Complement Ther Med. 21(1), 1-7.

112. Klingler, W., Velders, M., Hoppe, K., Pedro, M., Schleip, R. (2014): Clinical relevance of fascial tissue and dysfunctions. Curr Pain Headache Rep. 18(8), 439.

113. Koes, B. W. (2004): How to evaluate manual therapy: value and pitfalls of randomized clinical trials. Man Ther. 9(4), 183-184.

114. Kolahi, J., Bang, H., Park, J. (2009): Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. Community Dent Oral Epidemiol. 37(6), 477-484.

115. Kong, L. J., Zhan, H. S., Cheng, Y. W., Yuan, W. A., Chen, B., Fang, M. (2013): Massage therapy for neck and shoulder pain: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2013, 613279.

116. Kovacs, F. M., Abraira, V., Royuela, A., Corcoll, J., Alegre, L., Tomas, M., Mir, M. A., Cano, A., Muriel, A., Zamora, J., Del Real, M. T., Gestoso, M., Mufraggi, N. (2008): Minimum detectable and minimal clinically important changes for pain in patients with nonspecific neck pain. BMC Musculoskelet Disord. 9, 43.

117. Kristoffersen, A. E., Stub, T., Salamonsen, A., Musial, F., Hamberg, K. (2014): Gender differences in prevalence and associations for use of CAM in a large population study. BMC Complement Altern Med. 14, 463.

118. Kuleßa, R. (2017). *Manuelle Behandlung im widerstandsfreien Bereich*. Unpublished oral presentation. Cranio-Academy. Magdeburg.

119. La Touche, R., Fernandez-de-Las-Penas, C., Fernandez-Carnero, J., Diaz-Parreno, S., Paris-Alemany, A., Arendt-Nielsen, L. (2010): Bilateral mechanical-pain sensitivity over the trigeminal region in patients with chronic mechanical neck pain. J Pain. 11(3), 256-263.

120. Langevin, H. M., Sherman, K. J. (2007): Pathophysiological model for chronic low back pain integrating connective tissue and nervous system mechanisms. Med Hypotheses. 68(1), 74-80.

121. Lauche, R., Cramer, H., Langhorst, J., Dobos, G. (2013): Cupping for chronic nonspecific neck pain: a 2-year follow-up. Forsch Komplementmed. 20(5), 328-333.

122. Lauche, R., Cramer, H., Langhorst, J., Dobos, G., Gerdle, B. (2014a): Neck pain intensity does not predict pressure pain hyperalgesia: re-analysis of seven randomized controlled trials. J Rehabil Med, in press.

123. Lauche, R., Cramer, H., Langhorst, J., Michalsen, A., Dobos, G. J. (2014b): Reliability and Validity of the Pain on Movement Questionnaire (POM) in Chronic Neck Pain. Pain Med. 15(11), 1850-1856.

124. Lauche, R., Schuth, M., Schwickert, M., Ludtke, R., Musial, F., Michalsen, A., Dobos, G., Choi, K. E. (2016): Efficacy of the Alexander Technique in treating chronic non-specific neck pain: a randomized controlled trial. Clin Rehabil. 30(3), 247-258.

125. Le Bars, D. (2002): The whole body receptive field of dorsal horn multireceptive neurones. Brain Res Brain Res Rev. 40(1-3), 29-44.

126. Linton, S. J. (2000): A review of psychological risk factors in back and neck pain. Spine (Phila Pa 1976). 25(9), 1148-1156.

127. Lomba, J.A., Peper, C. (2013): Handbuch der Chiropraktik und strukturellen Osteopathie. Haug Fachbuch.

128. Long, A. F., MacKay, H. C. (2003): The effects of Shiatsu: Findings from a two-country exploratory study. Journal of Alternative and Complementary Medicine. 9(4), 539-547.

129. Low, E., Murray, D. M., O'Mahony, O., O'B Hourihane, J. (2008): Complementary and alternative medicine use in Irish paediatric patients. Ir J Med Sci. 177(2), 147-150.

130. Luborsky, L., Barber, J. P., Siqueland, L., Johnson, S., Najavits, L. M., Frank, A., Daley, D. (1996): The Revised Helping Alliance Questionnaire (HAq-II): Psychometric Properties. J Psychother Pract Res. 5(3), 260-271.

131. MacPherson, H., Tilbrook, H., Richmond, S., Woodman, J., Ballard, K., Atkin, K., Bland, M., Eldred, J., Essex, H., Hewitt, C., Hopton, A., Keding, A., Lansdown, H., Parrott, S., Torgerson, D., Wenham, A., Watt, I. (2015): Alexander Technique Lessons or Acupuncture Sessions for Persons With Chronic Neck Pain: A Randomized Trial. Ann Intern Med. 163(9), 653-662.

132. Magoun, H. I. (1997): Osteopathy in the Cranial Field. Denver: Sutherland Cranial Teaching Foundation, Inc.

133. Mann, J. D., Faurot, K. R., Wilkinson, L., Curtis, P., Coeytaux, R. R., Suchindran, C., Gaylord, S. A. (2008): Craniosacral therapy for migraine: protocol development for an exploratory controlled clinical trial. BMC Complement Altern Med. 8, 28.

134. Mataran-Penarrocha, G. A., Castro-Sanchez, A. M., Garcia, G. C., Moreno-Lorenzo, C., Carreno, T. P., Zafra, M. D. (2011): Influence of craniosacral therapy on anxiety, depression and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med. 2011, 178769.

135. Mayring, P. (2002): Einführung in die Qualitative Sozialforschung. Weinheim, Basel: Beltz.

136. Mazzeo, C.A. (2008): Nurturing the Mind/body Connection: A Phenomenological Analysis of Emotional Release in Massage Therapy. Ann Arbor: ProQuest, UMI Dissertations Publishing.

137. McLean, S. M., May, S., Klaber-Moffett, J., Sharp, D. M., Gardiner, E. (2010): Risk factors for the onset of non-specific neck pain: a systematic review. J Epidemiol Community Health. 64(7), 565-572.

138. Mehl-Madrona, L., Kligler, B., Silverman, S., Lynton, H., Merrell, W. (2007): The impact of acupuncture and craniosacral therapy interventions on clinical outcomes in adults with asthma. Explore (NY). 3(1), 28-36.

139. Melzack, R. (1999): From the gate to the neuromatrix. Pain. 6(6), S121-126.

140. Melzack, R., Wall, P. D. (1965): Pain mechanisms: a new theory. Science. 150(3699), 971-979.

141. Melzack, R., Wall, P. D. (1989): Textbook of Pain. London: Churchill Livingstone.

142. Mendell, L. M. (1966): Physiological properties of unmyelinated fiber projection to the spinal cord. Exp Neurol. 16(3), 316-332.

143. Merskey, H., Bogduk, N., The International Association for the Study of Pain. (1994): Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. Seattle: IASP Press.

144. Mesas, A. E., Gonzalez, A. D., Mesas, C. E., de Andrade, S. M., Magro, I. S., del Llano, J. (2014): The association of chronic neck pain, low back pain, and migraine with absenteeism due to health problems in Spanish workers. Spine (Phila Pa 1976). 39(15), 1243-1253.

145. Miana, L., Bastos, V. H., Machado, S., Arias-Carrion, O., Nardi, A. E., Almeida, L., Ribeiro, P., Machado, D., King, H., Silva, J. G. (2013): Changes in alpha band activity associated with application of the compression of fourth ventricular (CV-4) osteopathic procedure: a qEEG pilot study. J Bodyw Mov Ther. 17(3), 291-296.

146. Miller, F. G., Kaptchuk, T. J. (2008): The power of context: reconceptualizing the placebo effect. J R Soc Med. 101(5), 222-225.

147. Minasny, B. (2009): Understanding the process of fascial unwinding. Int J Ther Massage Bodywork. 2(3), 10-17.

148. Moher, D., Schulz, K. F., Altman, D. G. (2001): The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 357(9263), 1191-1194.

149. Monticone, M., Cedraschi, C., Ambrosini, E., Rocca, B., Fiorentini, R., Restelli, M., Gianola, S., Ferrante, S., Zanoli, G., Moja, L. (2015): Cognitive-behavioural treatment for subacute and chronic neck pain. Cochrane Database Syst Rev. (5), CD010664.

150. Moran, R. W., Gibbons, P. (2001): Intraexaminer and interexaminer reliability for palpation of the cranial rhythmic impulse at the head and sacrum. J Manipulative Physiol Ther. 24(3), 183-190.

151. Morhenn, V., Beavin, L. E., Zak, P. J. (2012): Massage increases oxytocin and reduces adrenocorticotropin hormone in humans. Altern Ther Health Med. 18(6), 11-18.

152. Müller-Busch, H.C. (2007): Kulturgeschichtliche Bedeutung des Schmerzes. In: B. Kröner-Herwig, J. Frettlöh, R. Klinger, P. Nilges (Eds.): Schmerzpsychotherapie. Grundlagen, Diagnostik, Krankheitsbilder, Behandlung (pp. 151-167). Heidelberg: Springer.

153. Myers, S. S., Phillips, R. S., Davis, R. B., Cherkin, D. C., Legedza, A., Kaptchuk, T. J., Hrbek, A., Buring, J. E., Post, D., Connelly, M. T., Eisenberg, D. M. (2008): Patient expectations as predictors of outcome in patients with acute low back pain. J Gen Intern Med. 23(2), 148-153.

154. Noll, D. R., Degenhardt, B. F., Stuart, M., McGovern, R., Matteson, M. (2004): Effectiveness of a sham protocol and adverse effects in a clinical trial of osteopathic manipulative treatment in nursing home patients. J Am Osteopath Assoc. 104(3), 107-113.

155. Nourbakhsh, M. R., Fearon, F. J. (2008): The effect of oscillating-energy manual therapy on lateral epicondylitis: a randomized, placebo-control, double-blinded study. J Hand Ther. 21(1), 4-13.

156. Pascual-Leone, A., Greenberg, L. S. (2007): Emotional processing in experiential therapy: why "the only way out is through.". J Consult Clin Psychol. 75(6), 875-887.

157. Patel, K. C., Gross, A., Graham, N., Goldsmith, C. H., Ezzo, J., Morien, A., Peloso, P. M. J. (2012): Massage for mechanical neck disorders. Cochrane Database Syst Rev. (9), CD004871.

158. Payne, P., Levine, P. A., Crane-Godreau, M. A. (2015): Somatic experiencing: using interoception and proprioception as core elements of trauma therapy. Front Psychol. 6(93).

159. Peloso, P., Gross, A., Haines, T., Trinh, K., Goldsmith, C. H., Burnie, S. (2007): Medicinal and injection therapies for mechanical neck disorders. Cochrane Database Syst Rev(3), CD000319.

160. Piron, H. (2003): Meditation und ihre Bedeutung für die seelische Gesundheit. Oldenburg: Bis.

161. Porges, S. W. (2001): The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol. 42(2), 123-146.

162. Price, C. J., Finniss, D. G., Benedetti, F. (2008): A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 59, 565-590.

163. Price, C. J., Thompson, E. A. (2007): Measuring dimensions of body connection: body awareness and bodily dissociation. J Altern Complement Med. 13(9), 945-953.

164. Rajendran, D., Bright, P., Bettles, S., Carnes, D., Mullinger, B. (2012): What puts the adverse in 'adverse events'? Patients' perceptions of post-treatment experiences in osteopathy--a qualitative study using focus groups. Man Ther. 17(4), 305-311.

165. Raviv, G., Shefi, S., Nizani, D., Achiron, A. (2009): Effect of craniosacral therapy on lower urinary tract signs and symptoms in multiple sclerosis. Complement Ther Clin Pract. 15(2), 72-75.

166. Roldan, C. J., Abdi, S. (2015): Quantitative sensory testing in pain management. Pain Manag. 5(6), 483-491.

167. Sack, M., Lempa, W., Steinmetz, A., Lamprecht, F., Hofmann, A. (2008): Alterations in autonomic tone during trauma exposure using eye movement desensitization and reprocessing (EMDR)--results of a preliminary investigation. J Anxiety Disord. 22(7), 1264-1271.

168. Sackett, D. L. (2004): Turning a blind eye: why we don't test for blindness at the end of our trials. BMJ. 328(7448), 1136.

169. Schafer, J. L. (1997): Analysis of Incomplete Mulitvariate Data. New York: Chapman and Hall.

170. Scherer, M., Chenot, J.F. (2016): [Neck pain - DEGAM clinical practice guideline]. Düsseldorf: Omikron.

171. Schleip, R. (2003): Fascial plasticity – a new neurobiological explanation. Part 2. J Bodyw Mov Ther. 7(2), 104-116.

172. Schleip, R., Zorn, A., Klingler, W. (2010): Biomechanical Properties of Fascial Tissues and Their Role as Pain Generators. J Musculoskelet Pain. 18(4), 393-395.

173. Schulz, K. F., Altman, D. G., Moher, D., Group, Consort. (2010): CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 340, c332.

174. Schwerla, F., Bischoff, A., Nurnberger, A., Genter, P., Guillaume, J. P., Resch, K. L. (2008): Osteopathic treatment of patients with chronic non-specific neck pain: a randomised controlled trial of efficacy. Forsch Komplementmed. 15(3), 138-145.

175. Scott, A., Khan, K. M., Cook, J. L., Duronio, V. (2004): What is "inflammation"? Are we ready to move beyond Celsus? Br J Sports Med. 38(3), 248-249.

176. Shea, B. J., Grimshaw, J. M., Wells, G. A., Boers, M., Andersson, N., Hamel, C., Porter, A. C., Tugwell, P., Moher, D., Bouter, L. M. (2007): Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 7, 10.

177. Shearer, H. M., Carroll, L. J., Wong, J. J., Cote, P., Varatharajan, S., Southerst, D., Sutton, D. A., Randhawa, K. A., Yu, H., Mior, S. A., van der Velde, G. M., Nordin, M. C., Stupar, M., Taylor-Vaisey, A. L. (2016): Are psychological interventions effective for the management of neck pain and whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Spine J. 16(12), 1566-1581.

178. Smeets, R. J., Beelen, S., Goossens, M. E., Schouten, E. G., Knottnerus, J. A., Vlaeyen, J. W. (2008): Treatment expectancy and credibility are associated with the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. Clin J Pain. 24(4), 305-315.

179. So, P. S., Jiang, Y., Qin, Y. (2008): Touch therapies for pain relief in adults. Cochrane Database Syst Rev(4), CD006535.

180. Sommerfeld, P., Kaider, A., Klein, P. (2004): Inter- and intraexaminer reliability in palpation of the "primary respiratory mechanism" within the "cranial concept". Man Ther. 9(1), 22-29.

181. Southerst, D., Nordin, M. C., Côté, P., Shearer, H. M., Varatharajan, S., Yu, H., Wong, J. J., Sutton, D. A., Randhawa, K. A., van der Velde, G. M., Mior, S. A., Carroll, L. J., Jacobs, C. L., Taylor-Vaisey, A. L. (2016): Is exercise effective for the management of neck pain and associated disorders or whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. The Spine Journal. 16(12), 1503-1523.

182. Staud, R. (2011): Effectiveness of CAM therapy: understanding the evidence. Rheum Dis Clin North Am. 37(1), 9-17.

183. Stecco, C., Day, J. A. (2010): The fascial manipulation technique and its biomechanical model: a guide to the human fascial system. Int J Ther Massage Bodywork. 3(1), 38-40.

184. Stecco, A., Meneghini, A., Stern, R., Stecco, C., Imamura, M. (2014): Ultrasonography in myofascial neck pain: randomized clinical trial for diagnosis and follow-up. Surg Radiol Anat. 36(3), 243-253.

185. Stocker, U. (2009): Komplementäre Therapien in der Psychiatrie. Pro Mente Sana Aktuell. 2, 20-22.

186. Stub, T., Salamonsen, A., Alraek, T. (2012): Is it possible to distinguish homeopathic aggravation from adverse effects? A qualitative study. Forsch Komplementmed. 19(1), 13-19.

187. Stumpf, W. E. (2006): The dose makes the medicine. Drug Discovery Today. 11(11), 550-555.

188. Tan, G., Craine, M. H., Bair, M. J., Garcia, M. K., Giordano, J., Jensen, M. P., McDonald, S. M., Patterson, D., Sherman, R. A., Williams, W., Tsao, J. C. (2007): Efficacy of selected complementary and alternative medicine interventions for chronic pain. J Rehabil Res Dev. 44(2), 195-222.

189. Tang, Y. Y., Ma, Y., Fan, Y., Feng, H., Wang, J., Feng, S., Lu, Q., Hu, B., Lin, Y., Li, J., Zhang, Y., Wang, Y., Zhou, L., Fan, M. (2009): Central and autonomic nervous system interaction is altered by short-term meditation. Proc Natl Acad Sci U S A. 106(22), 8865-8870.

190. Testut, L., Sperino, G. (1923): Anatomia umana (anatomia descrittiva - istologia - sviluppo). Torino: Unione Tipografico-Editrice Torinese.

191. Tölle, T. R., Berthele, A. (2007). Biologische Mechanismen der Chronifizierung – Konsequenzen für die Prävention. In B. Kröner-Herwig, J. Frettlöh, R. Klinger, P. Nilges (Eds.), Schmerzpsychotherapie. Grundlagen, Diagnostik, Krankheitsbilder, Behandlung (pp. 81-102). Heidelberg: Springer.

192. Tong, A., Sainsbury, P., Craig, J. (2007): Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 19(6), 349-357.

193. Trowbridge, C. (1991): Andrew Taylor Still, 1828-1917. Truman State University Press.

194. Twiss, C. O., Fischer, M. C., Nitti, V. W. (2007): Comparison between reduction in 24-hour pad weight, International Consultation on Incontinence-Short Form (ICIQ-SF) score, International Prostate Symptom Score (IPSS), and Post-Operative Patient Global

Impression of Improvement (PGI-I) score in patient evaluation after male perineal sling. Neurourol Urodyn. 26(1), 8-13.

195. Uchida, S., Budgell, B. (2009): Somato-Autonomic Reflex. In: M. D. Binder, N. Hirokawa, U. Windhorst (Eds.): Encyclopedia of Neuroscience (pp. 3767-3770). Berlin, Heidelberg: Springer.

196. Upledger, J.E. (1990): Somato Emotional Release and Beyond. Upledger Inst.

197. Upledger, J.E. (1997): Your Inner Physician and You: Craniosacral Therapy and Somatoemotional Release. North Atlantic Books.

198. Upledger, J.E., Vredevoogt, J. (1983): Craniosacral therapy. Seattle: Eastland Press.

199. van der Wal, J. (2009): The architecture of the connective tissue in the musculoskeletal system-an often overlooked functional parameter as to proprioception in the locomotor apparatus. Int J Ther Massage Bodywork. 2(4), 9-23.

200. van Saase, J. L., van Romunde, L. K., Cats, A., Vandenbroucke, J. P., Valkenburg, H. A. (1989): Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis. 48(4), 271-280.

201. Vernon, H., Humphreys, B. K., Hagino, C. (2006): The outcome of control groups in clinical trials of conservative treatments for chronic mechanical neck pain: a systematic review. BMC Musculoskelet Disord. 7, 58.

202. Vernon, H., MacAdam, K., Marshall, V., Pion, M., Sadowska, M. (2005): Validation of a sham manipulative procedure for the cervical spine for use in clinical trials. J Manipulative Physiol Ther. 28(9), 662-666.

203. Vincent, K., Maigne, J. Y., Fischhoff, C., Lanlo, O., Dagenais, S. (2013): Systematic review of manual therapies for nonspecific neck pain. Joint Bone Spine. 80(5), 508-515.

204. von Mohr, M., Kirsch, L. P., Fotopoulou, A. (2017): The soothing function of touch: affective touch reduces feelings of social exclusion. Sci Rep. 7(1), 017-13355.

205. von Peter, S., Ting, W., Scrivani, S., Korkin, E., Okvat, H., Gross, M., Oz, C., Balmaceda, C. (2002): Survey on the use of complementary and alternative medicine among patients with headache syndromes. Cephalalgia. 22(5), 395-400.

206. Vos, C., Verhagen, A., Passchier, J., Koes, B. (2007): Management of acute neck pain in general practice: a prospective study. Br J Gen Pract. 57(534), 23-28.

207. Vrontou, S., Wong, A. M., Rau, K. K., Koerber, H. R., Anderson, D. J. (2013): Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. Nature. 493(7434), 669-673.

208. Walker, B. F., French, S. D., Grant, W., Green, S. (2011): A Cochrane review of combined chiropractic interventions for low-back pain. Spine (Phila Pa 1976). 36(3), 230-242.

209. Weiss, T., Schaible, H.-G. (2008). Strukturen der Nozizeption und der Schmerzverarbeitung. In F. van den Berg (Ed.), Angewandte Physiologie 4. Schmerzen verstehen und beeinflussen (pp. 6-34). Stuttgart: Thieme.

210. White, I. R., Royston, P., Wood, A. M. (2011): Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine. 30(4), 377-399.

211. WHO Collaborating Centre for Drug Statistics Methodology. (2013): Guidelines for ATC classification and DDD assignment 2014. Oslo: Norwegian Institute of Public Health.

212. Wong, J. J., Cote, P., Ameis, A., Varatharajan, S., Varatharajan, T., Shearer, H. M., Brison, R. J., Sutton, D., Randhawa, K., Yu, H., Southerst, D., Goldgrub, R., Mior, S., Stupar, M., Carroll, L. J., Taylor-Vaisey, A. (2016): Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J. 25(1), 34-61.

213. Woodhouse, A., Pape, K., Romundstad, P. R., Vasseljen, O. (2016): Health care contact following a new incident neck or low back pain episode in the general population; the HUNT study. BMC Health Serv Res. 16, 81.

214. Woolf, C. J., Salter, M. W. (2000): Neuronal plasticity: increasing the gain in pain. Science. 288(5472), 1765-1769.

215. Yang, H., Haldeman, S., Nakata, A., Choi, B., Delp, L., Baker, D. (2015): Work-related risk factors for neck pain in the US working population. Spine (Phila Pa 1976). 40(3), 184-192.

216. Yeung, W. F., Chung, K. F., Poon, M. M., Ho, F. Y., Zhang, S. P., Zhang, Z. J., Ziea, E. T., Wong, V. T. (2012): Acupressure, reflexology, and auricular acupressure for insomnia: a systematic review of randomized controlled trials. Sleep Med. 13(8), 971-984.

217. Yu, J. S., Zeng, B. Y., Hsieh, C. L. (2013): Acupuncture stimulation and neuroendocrine regulation. Int Rev Neurobiol. 111, 125-140.

218. Zusman, M., Moog-Egan, M. (2008). Neurologisch begründete Mechanismen der Schmerzlinderung durch Physiotherapie. In F. van den Berg (Ed.), Angewandte Physiologie 4. Schmerzen verstehen und beeinflussen (pp. 227-229). Stuttgart: Thieme.

8 Appendix

8.1 Index of abbreviations

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AOR	Adjusted odds ratios
B	Regression coefficient
CEQ	Credibility/Expectancy Questionnaire
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COREQ	Consolidated Criteria for Reporting Qualitative Studies
CST	Craniosacral Therapy
D	Cohen's d: effect size
DDD	Defined Daily Doses
Δ	Delta: between-group difference
ERDA	Emotional/Rational Disease Acceptance Questionnaire
FEW	Questionnaire for Assessing Subjective Physical Well-being
HADS	Hospital Anxiety and Depression Scale
HAQ	Helping Alliance Questionnaire
I^2	Statistical heterogeneity
N	Number of subjects
NA	Not applicable
NDI	Neck Disability Index
P	Probability to obtain the observed or more extreme results when the H_0 is true
PGI-I	Patients' Global Impression of Improvement
POM	Pain on Movement Scale
PPT	Pressure pain threshold
PSQ	Perceived Stress Questionnaire
SBC	Scale of Body Connection
SD	Standard deviation
SE	Standard error
SF-12	Short Form Health Survey
SIG	Significance
SMD	Standard mean difference
VAS	Visual Analogue Scale

8.2 List of figures

Figure 1. Template of the body image drawing ... 25
Figure 2. Consort flow chart ... 29
Figure 3. Concurrent analgesics use (mean ± SD) during the intervention period ... 32
Figure 4. Predictive power (AORs ± 95% CI) of credibility and therapeutic alliance measures ... 33
Figure 5. Effects (mean ± SD) on pain intensity ... 34
Figure 6. Effects (mean ± SD) on pain on movement ... 37
Figure 7. Effects (mean ± SD) on pressure pain thresholds at the point of maximum pain ... 37
Figure 8. Effects (mean ± SD) on pressure pain thresholds bilaterally at the trapezius muscle ... 38
Figure 9. Effects (mean ± SD) on functional disability ... 38
Figure 10. Effects (mean ± SD) on physical quality of life ... 38
Figure 11. Effects (mean ± SD) on body awareness ... 39
Figure 12. Effects (mean ± SD) on anxiety ... 39
Figure 13. Effects on global improvement ... 40
Figure 14. Word frequency analysis ... 40
Figure 15. Body image drawing of patient 42 at baseline and week 8 ... 41
Figure 16. Body image drawing of patient 49 at baseline and week 8 ... 41

8.3 List of tables

Table 1. Semi-structured interview guide 26
Table 2. Quantitative data: drop-out analysis 30
Table 3. Qualitative data: drop-out analysis 30
Table 4. Sample characteristics at baseline 31
Table 5. Logistic regression analysis 33
Table 6. Responder analysis of the primary outcome 34
Table 7. Effects (mean ± SD) of Craniosacral Therapy in comparison with sham 35
Table 8. Local and systemic physical responses 42
Table 9. Gain in body perception and awareness 43
Table 10. Emotional reprocessing 44
Table 11. Access to spiritual experiences 45
Table 12. Cognitive restructuring 46
Table 13. Changes in coping behavior 47
Table 14. Socio-economic impact 47
Table 15. Safety 48