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TITLE PAGE

Preliminary evidence of Regional Interdependent Inhibition, using a 'Diaphragm Release' to specifically induce an immediate hypoalgesic effect in the cervical spine.

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ABSTRACT

In clinical practice, Osteopaths and Manual Therapists commonly direct treatment towards the diaphragm by the use of a 'Diaphragm Release'. Currently, there is paucity within the literature to support the use of this technique, specifically in pain outcomes. This research aims to support a neurophysiological mechanism based upon the osteopathic principle "The body is a unit". Demonstrating that directing treatment to distal tissue which is neurologically related can reduce pain in the originating spinal segments**.** This study investigated the immediate hypoalgesic effects of a 'Diaphragm Release' on pain pressure thresholds in the cervical spine. A single-blind, randomised, sham-controlled, repeated measures within subject, crossover design was conducted on 17 asymptomatic subjects. Pain pressure thresholds were measured bilaterally in the C4 paraspinal musculature, lateral end of the clavicle and upper third of the tibialis anterior before and after a 'Diaphragm Release'. Results demonstrated a statistically significant hypoalgesic effect was only found in the spinal segment C4 in both the right (p= 0.016) and left (p= 0.004) sides. Averaging the hypoalgesic effect from both sides equates to a 17.17% change which is considered clinically significant, the effect magnitude was calculated to be small but educationally significant for the right (*d*= 0.26) and left (*d*= 0.40) sides. This study supports a novel neurophysiological mechanism, Regional Interdependent Inhibition, to induce a hypoalgesic state at segmentally related spinal segments, specifically C4. Suggesting that directing treatment towards the diaphragm, using a 'Diaphragm Release', could induce an immediate clinically and statistically significant hypoalgesic effect local to the fourth cervical segment due to its relationship with the phrenic nerve.

KEYWORDS

Osteopathy; Manual Therapy; Neurophysiological Mechanism; Diaphragm; Pain Pressure Thresholds; Regional Inhibitory Interdependence.

INTRODUCTION

Osteopathy and Manual Therapy (MT) traditionally uses a biomechanical and structural model to assess, diagnose and treat patient's musculoskeletal conditions. It is suggested through muscle imbalances, structural or spinal asymmetry or restrictions the body develops painful musculoskeletal conditions (Chila 2010; Lederman 2011). The commonly used term '*Tissue Release*' in relation to treatment outcomes of muscular imbalances is typically approached from a mechanistic and structural perspective (Schleip 2003). Connective tissue is known to lengthen under static load due to its innate viscoelastic properties; however, this effect is transient and dependent upon duration and mode of stretch (Chaudhry et al 2007; Solomonow, 2009). The palpable phenomenon of a '*Release*' that is described by clinicians can be explained by a modification of nociceptive sensation or reflexive changes (Chaudhry et al 2008; Konrad & Tilp 2014; Weppler & Magnusson 2010). The Pain Gate Theory proposed 50 years ago by Melzack & Wall, (1965) provided a landmark mechanism and was the genesis for understanding pain modulation from non-noxious sensory input. The mechanism has been expanded upon in recent years through the neuromatrix (Melzack 2001) and the neurophysiological mechanism which includes the peripheral mechanism, spinal mechanism and supraspinal mechanism (Bialosky et al 2009). The neuromatrix theory describes a complex framework active in pain processing through a network of neurones or 'neurosignature'. From sensory, affective and cognitive inputs a multidimensional pain experience emerges with synchronous behavioural and homeostatic responses. Yet, specific to the neurophysiological effects of MT, the spinal mechanism describes pain modulation due to mass sensory inputs from mechanoreceptors throughout the techniques to inhibit the spinal level (Bialosky et al., 2009; Boal & Gillette, 2004; Pickar, 2002). Through the expansion of the Pain Gate Theory, the influence that placebo plays as a part of contextual effects in pain outcomes in clinical practice is significant (Bialosky et al 2011; Kaptchuk et al 2008; Quintner et al 2014). It has been suggested that manual therapists should take steps to maximize placebo effects within ethical limitations (Bialosky et al 2011). Which leads Ernst & Harkness (2001) to rightly question if interventions used in manual therapy act through other mechanisms beside the placebo effect? Understanding the neurophysiological mechanism behind the effectiveness of MT would not only help identify which patients are likely to respond but also increase the acceptance of techniques by health care providers who may view them as unscientific (Bialosky et al 2009). Evidence by Bialosky et al (2009) and Voogt et al (2014) supports this shift toward a neurophysiological explanation of the mechanism behind the effectiveness of MT, incorporating the brain, spinal cord and peripheral nerves; rather than altering the biomechanics and the physiological structure of connective tissue.

Whether or not the neurophysiological mechanism behind MT is specific or non-specific in its effects is questionable. That is to say, does one intervention create an intended effect to a particular region that is neurologically related or does it cause a systemic effect throughout the nervous system effecting tissues globally?

Immediate hypoalgesia can be produced in specific local spinal segments following MT interventions. A study by George et al (2006), found evidence of local dorsal horn pain inhibition following spinal manipulation in the lumbar spine of asymptomatic subjects. Sterling et al (2001), identified that spinal manipulation of one side of the cervical spine induced side specific local modulation of mechanical nociception as measured by algometry. However, some studies have discovered that spinal manipulation and peripheral mobilisation can induce a significant widespread state of hypoalgesia that is non-specific (Bialosky et al 2008; Krouwel et al 2010; Willett et al 2010).

Collectively, these studies typify a 'descending' hypoalgesic mechanism of descending inhibitory pathways and subsequent dorsal horn inhibition. Meaning, an intervention is directed towards the spine and pain outcome measures are taken either at the site of application (George et al 2006; Sterling et al 2001) or at a neurologically related distal site (Fernández-Carnero et al 2011; Fernández-Carnero et al, 2008; Vicenzino et al 1996). Osteopathic textbooks follow similar logic, suggesting, if a patient presents with diaphragm dysfunction, one should direct treatment towards the cervical spine, specifically C3-5 (Chila 2010; DiGiovanna et al 2005; Parsons & Marcer 2005; Sammut & Searle-barnes 1998). The diaphragm is innervated by the phrenic nerve, variably arising from multiple spinal segments from the third to sixth cervical segments, with the fourth segment indispensable (Banneheka, 2008). This relationship between the cervical spine, diaphragm can be thought of as Regional Interdependence, an adaption of the longstanding principle that the body is a unit. A notion which describes the body as a complex functional unit, made up of physical, cognitive and spiritual aspects. Where a physiological system is continuous and compensation occurs throughout the body to adapt and maintain homeostasis. Regional Interdependence and the principle that the body is a unit explains how irritation and dysfunction of the diaphragm is responsible for the common palpatory findings of somatic dysfunction and facilitated segments in the cervical spine (Ward 2003 p. 393,712). Normalisation of the cervical facilitated segments by inhibiting the hyperactive and reflexive spinal levels by directing MT towards the diaphragm can be understood as an 'ascending' hypoalgesic mechanism, Regional Inhibitory Interdependence (RII). In a wider context, RII may demonstrate how MT techniques directed towards distal tissue could induce hypoalgesic effects specific to its segmental origins, with the proviso that a direct neurological relationship exists.

One study that utilises a similar mechanism was conducted by McSweeney et al (2012). This study found a statistically significant hypoalgesic effect specific to the L1 spinal segment after visceral mobilisation of the sigmoid colon. This supports the concept behind RII by suggesting pain modulation can be influenced at specific spinal levels after MT is directed to distal tissues that are segmentally related. Although direct comparisons cannot be made in non-human studies, Malisza et al (2003) identified crucial evidence for the existence of RII existing in rat subjects injected with capsaicin into the ankle joint using functional MRI. This study found that after peripheral mobilisation of the ankle, there was decreased activation of the dorsal horn of the spinal cord when the paw was touched.

The primary outcome for this study is to identify any statistically significant changes in pain pressure thresholds in the neck immediately after a 'Diaphragm Release' and aims to provide preliminary evidence of a RII neurophysiological mechanism to alleviate cervical spine pain, specifically C4, by directing treatment to the diaphragm. This study also took into consideration the findings of a recent study investigating the opinions of research and evidence based practice in UK Osteopaths; '*conducting research to better understand the principles that we know to be clinically effective...it is of paramount clinical importance that any research carried out should be focused on clinical cost effectiveness of osteopathic clinical practice*' (Humpage 2011 p. 52).

METHODS

Subjects

Twenty asymptomatic participants were recruited for this study from a sample of 2nd-4th year Osteopathic students. Participants provided written informed consent, completing a medical case history form and a post experimental questionnaire. Participants were invited to take part in the study using posters and information sheets in breakout rooms and via E-mail. Participants were excluded if deemed unsuitable discovered from case history, failed to attend the first session or took part in rigorous exercise or received manual therapy in the previous 3 days. The College of Human and Health Sciences at Swansea University granted ethical approval for this study in October 2014. All experimental conditions were performed by a registered osteopath with over 10 years of clinical experience (Researcher 1).

Design

This proof-of-concept experiment method consisted of a single blind, randomised, sham-controlled, repeated measures within subject, crossover study design.

Randomisation

Prior to the study commencing, participants were randomly allocated an intervention order, using a computer research randomiser (Urbaniak & Plous 2007). An intervention code was produced: control, sham and experimental condition (0, 1 & 2). Each participant's randomised intervention order was placed in an opaque sealed envelope, which was opened by Researcher 1 after Researcher 2 had collected the pre-intervention Pain Pressure Threshold (PPT) measurements. Researcher 1 created an allocation code to determine which number referred to each intervention used throughout the study; this code was also sealed in an opaque envelope and was opened after the study was completed, as validated by Suresh (2011).

Equipment / setting

PPT's were measured using a digital algometer (Salter Force Gauge EFG MK2). The algometer was calibrated by the manufacturer and uses a $1cm^2$ rubber tip. Data was collected over a two-week period, the participants attended on three separate occasions, at least 3 days apart. Once randomised, the participants attended the room at the same time slot, receiving a different intervention each time. The experiment took place in a quiet (10x10m) room, with a maintained ambient temperature (20˚C), one couch (Plinth 2000) and no clock.

Independent Variables

procedure

Sites for the pain pressure threshold readings were located and marked as a "dot" with a surgical skin marking pen. Instructions were given to each subject prior to the start of the test about the measuring procedure. Please note that PPT were measured on both sides of the body for the selected sites. The PPT site locations were cervical spine (0.5cm lateral to both sides of the spinous process of C4); clavicles (superior surface the lateral third, directly superior to the coracoid process) and tibialis anterior (upper third of the muscle belly). (please see dependent measure for further details of PPT dependent variable measurements). The participants were told to state, "Yes" immediately when the pressure sensation turned into an uncomfortable sensation, the pressure was stopped and a reading made once the algometer was removed from the body. Researcher 2 applied pressure through the algometer at a steady rate of 5 N/s-1. Readings were taken from each site between 30-second breaks.

Participants were invited into the Experiment Room with Researcher 2 who took the pre-intervention PPT measurements and exited. Researcher 1 entered and performed one of the randomly assigned interventions for that participant. Researcher 1 left the room for Researcher 2 to re-enter and take post-intervention PPT measurements. Each experimental condition was performed for 90 seconds to 2 minutes, Researcher 1 was instructed to only communicate in order to instruct the patient and gain consent. A post-experimental questionnaire was implemented to determine the success of subject blinding.

Experimental Conditions

diaphragm

Participants receiving the diaphragm intervention were told; "*Today, you will be receiving an osteopathic technique commonly taught and used in Osteopathic practice that will be targeting the diaphragm. Breathe normally and relax*". Researcher 1 then located the xiphoid process and the costal arch and sank fingers bilaterally, posterior and laterally under the rib cage, emphasising contact to the posterior surface of the lower ribs if possible on expiration, as shown in Figure 1 & 2 and in *Foundations of Osteopathic Medicine* (Ward, Page 1066).

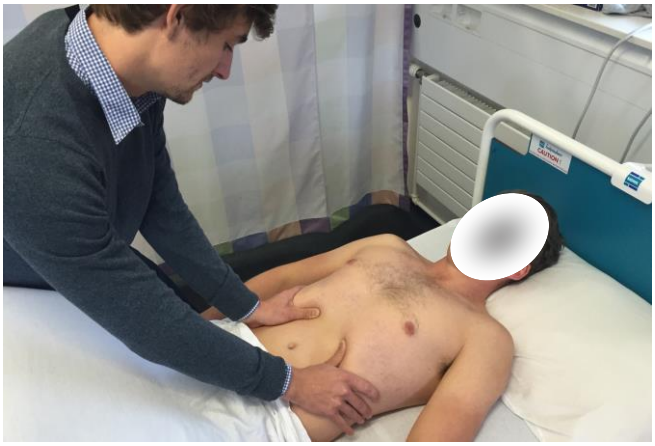

Figure 1. 'Diaphragm Release' as shown in the Foundations of Osteopathic Medicine (Ward, 2003, p. 1066).

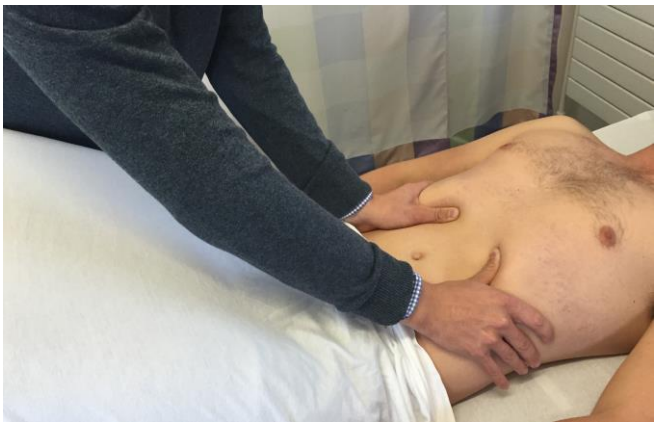

Figure 2. Close up of 'Diaphragm Release' emphasizing contact up and against the posterior surface of the lower ribs on expiration.

Rational for "Diaphragm Release": In animal subjects, mechanical stimulation of the diaphragm from manual pressure into the thoracic cavity, was shown to activate mechanoreceptors in the diaphragm and subsequently large diameter afferent neurones in the phrenic nerve (Zhang & Davenport, 2003). The diaphragm is able to project information regarding alterations in mechanical tension and pressure to the spinal cord, similar to limb muscles (Holt, Dalziel, & Davenport, 1991). By electrically stimulating afferent neurones in the phrenic nerve, neuronal activity in the dorsal horn was observed, specifically in the originating spinal segments (Chou & Davenport, 2005). Phrenic afferent neurons are also known to synapse with intermediate inhibitory neurones (Lee & Fuller, 2011), 2011), similar to the pain gate theory (Melzack & Wall, 1965). This experimental evidence on animal subjects provides clear evidence to suggest that mechanical provocation to the diaphragm would activate mechanoreceptors. This information travels via large diameter afferent neurones to the dorsal horn of predominantly the fourth cervical segment, where they would synapse with intermediate inhibitory neurones. This

would shift the balance in regards to the pain gate theory and effectively "close" the gate, resulting in hypoalgesia in somatic tissue supplied by the fourth cervical segment.

sham

Participants receiving the Sham intervention were told; "*Today, you will be receiving a gentle Balanced ligamentous tension technique commonly taught and used in Osteopathic practice that will be targeting the diaphragm*. *Breathe normally and relax.*" Researcher 1 then located the anterior costal margin and rested his hands on the skin, engaging no therapeutic barriers. A 'functional technique' sham is supported by previous research investing manual therapy techniques and PPT (Hamilton et al 2007; Saíz-Llamosas et al 2009).

control

Participants receiving the control intervention were told; "*Today, we just want you to breathe normally and relax*". Researcher 1 was merely present in the room.

Dependant Variables

reason for use

Pressure algometry was chosen to quantify the change in the participant's pain perception in this study due to its practical and economical advantage. Previous research investigating the hypoalgesic effects of MT interventions has shown algometry to be very reliable with good-excellent intra-observer reliability in both symptomatic and asymptomatic populations (Cathcart & Pritchard 2006; Chesterton et al 2007; Cheung et al 2013; La Touche et al 2009; McSweeney et al 2012; Potter et al 2006; Ruiz-Sáez et al 2007; Ylinen et al 2007). The reliability is enhanced when all measurements are taken by one examiner and applied at a steady rate (Nussbaum & Downes, 1998); the chosen rate of application is similar to that in previous studies investigating MT interventions (Fryer et al 2004; McSweeney et al 2012; Vicenzino et al 2001). PPT were measured on both sides of the body for the selected sites, previous studies have demonstrated no statistical differences in PPT values between right and left sides of the body (Fischer 1987; Vanderweeen et al 1996). Regional differences of PPT measurements have been identified with PPT values increasing in the caudal direction, it is suggested that this is due to the lower density of mechanoreceptors and nociceptors caudally (Fischer 1987; Keating et al 2001; Vanderweeen et al 1996).

site location

PPT site locations selected were cervical spine (0.5cm lateral to both sides of the spinous process of C4); clavicles (superior surface the lateral third, directly superior to the coracoid process) and tibialis anterior (upper third of the muscle belly). Some studies have described that algometry readings over bone display a lower mean PPT in comparison to muscle (Keating et al 2001; Ohrbach & Gale 1989); however, some authors argue this and report no differences of algometry readings over bone or muscle (Kosek et al 1993).

rationale for site selection

Algometry sites in the cervical spine, clavicle and tibialis anterior were chosen to observe any local or systemic neurophysiological changes after the 'Diaphragm Release'. Sites in the cervical spine were chosen in order to best observe any local neurophysiological changes after the 'Diaphragm Release' as the action potentials are conducted via the afferent fibres of the phrenic nerve, mostly entering at the fourth cervical segment (C4) (Banneheka, 2008). Sites in the clavicles were to chosen to best observe any neurophysiological changes in all tissue neurologically supplied by the fourth cervical segment, cutaneous supply of both the shoulder and clavicle is via supraclavicular nerves (C4). Additionally, the algometry sites in the clavicles were carefully selected to lie within an area where patients perceive shoulder pain and referrals from the diaphragm (Bayam et al 2011; Gulick 2006; Magee 2014, p. 349). Sites in the tibialis anterior were chosen to rule out any systemic neurophysiological effects of the 'Diaphragm Release' as the innervation of the tibialis anterior is unrelated to the cervical spine and the diaphragm. The use of tibialis anterior as a distal site has been supported in previous studies investigating neck pain to distinguish a local or widespread effect (Cheung et al 2013; Chien et al 2009; Johnston et al 2008; Sterling et al 2002).

data

Microsoft Excel (2013) was used to store the data and calculate the demographic statistics. SPSS package (version 21.0) was used for further analysis of data.

reliability

The intra-rater reliability for pressure algometry was calculated by comparing the three pre-intervention PPT's on each side at each site, as described by Fleiss (1987). The classification system by Shrout & Fleiss (1979) was used in this study to determine the level of reliability: >0.75, excellent; 0.6-0.75, good; 0.4-0.59, fair; and <0.4, poor. A 2-way analysis of variance using a random effects model was used to calculate intra-rater reliability.

statistical analysis

Treatment Effect: Pre- and post-intervention PPT values in each site were compared against each other using a paired samples *t*-test with a 95% confidence interval. A two tailed probability of <0.05 was regarded as significant.

Between Intervention Effects: A two way (2x3) within-subjects repeated measures analysis of variance (ANOVA) was used to ascertain if there was any interaction between the three independent variables. The three independent variables for the dependant variable of pressure algometry were: three levels of treatments (control, sham, and diaphragm); two levels of site sides at different times (pre- and post-intervention). Separate ANOVA's were run independently for both right and left sides. At this stage it would be discovered that there was either a significant or non-significant difference between interventions. If a statistically significant interaction exists, post-intervention measurements were subtracted from pre-intervention measurements to calculate the change post-intervention, this value becomes the dependant variable for the following one-way ANOVA. The planned comparisons for the one way ANOVA were between diaphragm and control, diaphragm and sham and sham and control. The dependant variable (difference between pre- and post-intervention measurements) was analysed with a one-way between group within-subjects ANOVA against the three independent variables (control, sham and diaphragm) to answer the planned comparison. A scheffe post-hoc comparison was used to compare the differences between the mean change in PPT post-intervention within the three intervention groups. The mean significance was set to be significant at the level of <0.05.

Between Site Effects: A two way (2x3) within-subjects repeated measures analysis of variance (ANOVA) was used to ascertain if there was any interaction between the three independent variables. The three independent variables for the dependant variable of pressure algometry were: three levels of sites (cervical spine, clavicle and tibialis anterior); two levels of site sides at different times (pre- and post-intervention). Separate ANOVA's were run independently for both right and left sides. At this stage it would be discovered that there was either a significant or non-significant difference between interventions. If a statistically significant interaction exists, post-intervention measurements were subtracted from pre-intervention measurements to calculate the change post-intervention, this value becomes the dependant variable for the following one-way ANOVA. The planned comparisons for the one-way ANOVA were between cervical spine and clavicle, cervical spine and tibialis anterior and clavicle and tibialis anterior. The dependant variable (difference between pre- and post-intervention measurements) was analysed with a one-way between group within subject ANOVA against the three independent variables (cervical spine, clavicle and tibialis anterior) to answer the planned comparison. A scheffe post-hoc comparison was used to compare the differences between the mean change in PPT post-intervention within the three intervention groups. The mean significance was set to be significant at the level of <0.05.

***Effect Sizes**:* Effect-size estimates were calculated to allow interpretation of results in a more functional and meaningful way by evaluating the magnitude of effect or strength of a relationship. Effect size is commonly interpreted in the literature using benchmarks set by Cohen (1988). Cohen suggests that a larger effect size has a bigger impact from the intervention. A correlation of 1.00-0.80 is large, 0.79-0.50 is moderate, 0.49-0.20 is small, and 0.19-0.00 is no effect. However, Wolf (1986), suggested that 0.25 indicates an educationally significant effect and 0.50 would indicate a clinically significant effect. Both interpretations were taken into consideration in the analysis of the effect size.

RESULTS

Participants

Three subjects were excluded from the study: two subjects failed the medical case history due to recent surgery and one subject failed to attend the initial testing date, and, due to time restrictions, was excluded. All of the 17 included participants reported no adverse effects from either the interventions or the PPT measurements. The basic demographic data of the included participants is displayed in Table 1.

Subject blinding

A post-experimental questionnaire was implemented to determine the success of subject blinding. No subjects were able to identify the diaphragm intervention as the real aim of the study when questioned against the sham intervention.

Intra-Rater Reliability

The mean ICC was calculated to be excellent in the right and left cervical spine as 0.870, 95% CI (0.707, 0.949) and 0.901, 95% CI (0.777, 0.961) respectively; the consistency between right and left sides were also excellent, calculated as 0.939, 95% CI (0.879, 0.975), see Table 2.

Treatment Effect

A statistically significant increase between PPT values pre- (M=31.847, SD=15.480) and post-intervention (M=36.176, SD=18.311) in the right cervical spine site was shown after the 'Diaphragm Release'; $t(16)= -2.70$, p= 0.016, 95% CI (-7.732, -0.927). Similarly, a statistically significant difference between PPT values pre- (M=30.412, SD=14.145) and post- intervention (M=36.724, SD=18.120) in the left cervical spine site was identified after the 'Diaphragm Release'; $t(16)= -3.31$, p= 0.004, 95% CI (-10.353, -2.270), see Figure 3. This was equivalent of a 13.59% and 20.75% change for the right and left side of the cervical spine after the 'Diaphragm Release'. No statistically significant increases in PPT were observed in both sides of the clavicle or tibialis anterior for any experimental condition.

After the sham intervention a significant difference between the PPT values pre- (M=29.730, SD=12.590) and post-intervention (M=31.750, SD=13.220) occurred only in the right cervical spine site; $t(16)= -2.34$, p= 0.033, 95% CI (-

3.86, -0.19), equivalent to a change of 6.81%. No significant difference between the PPT values pre- (M=32.871, SD=14.877) and post-intervention (M=33.782, SD=13.171) was found after the sham intervention in the left cervical spine site; *t*(16)= -.61, p= 0.548, 95% CI (-4.064, 2.240).

No significant differences were observed between the PPT values pre- (M=28.071, SD=11.297) and post-intervention (M=26.912, SD=9.422) in the right cervical spine after the control intervention; *t*(16)= 0.50, p= 0.504, 95% CI (-2.436, 4.754). Similarly, no significant difference were observed between the PPT values pre- (M=26.800, SD=27.441) and post-intervention (M=27.441, SD=10.129) in the left cervical spine after the control intervention; *t*(16)= -0.51, p= 0.620, 95% CI (-3.327, 2.044).

No significant differences were observed between the right (M=28.071, SD=11.297) and left (M=26.800, SD=27.441) pre-intervention PPT values in the cervical spine in the control interventions; *t*(16)= 0.97, p= 0.344. No significant differences were observed between the right (M=29.730, SD=12.590) and left (M=32.871, SD=14.877) pre-intervention PPT values in the cervical spine in the sham interventions; *t*(16)= -1.54, p= 0.143. No significant differences were observed between the right (M=31.847, SD=15.480) and left (M=30.412, SD=14.145) pre-intervention PPT values in the cervical spine in the diaphragm interventions; *t*(16)= 0.53, p= 0.601.

Between Intervention Effects

Two separate, two-way within-subjects repeated measures ANOVAs (2x3) identified a significant difference in the cervical spine between the three independent variables (control, sham and 'Diaphragm Release'), for pre and post interventions in both right (F(2,48) = 3.673, p= 0.033) and left (F(2,48) = 4.120, p= 0.022), see Figure 4. Further analysis using a one-way ANOVA and a Scheffe post-hoc comparison identified a significant difference between the right (F(2,48) = 3.67, p= 0.034) and left (F(2,48) = 4.120, p= 0.048) PPT mean difference only after the 'Diaphragm Release' compared to the control. No significant differences were observed between the right (F(2,48) = 3.67, p= 0.530) and left (F(2,48) = 4.120, p= 0.063) PPT mean difference after the 'Diaphragm Release' compared to the sham. No significant differences were observed between the right (F(2,48) = 3.67, p= 0.303) and left (F(2,48) = 4.120, p= 0.993) PPT mean difference after the sham compared to the control.

Between Site Effects

Two separate, two-way within-subjects repeated measures ANOVA (2x3) identified a non-significant difference between the three independent variables (cervical spine, clavicle and tibialis anterior) immediately after the 'Diaphragm Release' in both right (F(2,48) = 2.597, p= 0.085) and left (F(2,48) = 1.532, p= 0.227) sites, see Figure 5.

Effect Size

A small and educationally significant hypoalgesic effect was shown in both the right (*d* =0.260) and left (*d*= 0.400) cervical spine sites after a 'Diaphragm Release', see Figure 6. No hypoalgesic effect was shown in the right (*d* =0.160) and left (*d* = 0.070) cervical spine site after the sham intervention. No hypoalgesic effect was shown in the right (*d* =0.110) and left (*d* = 0.060) cervical spine site after the control intervention.

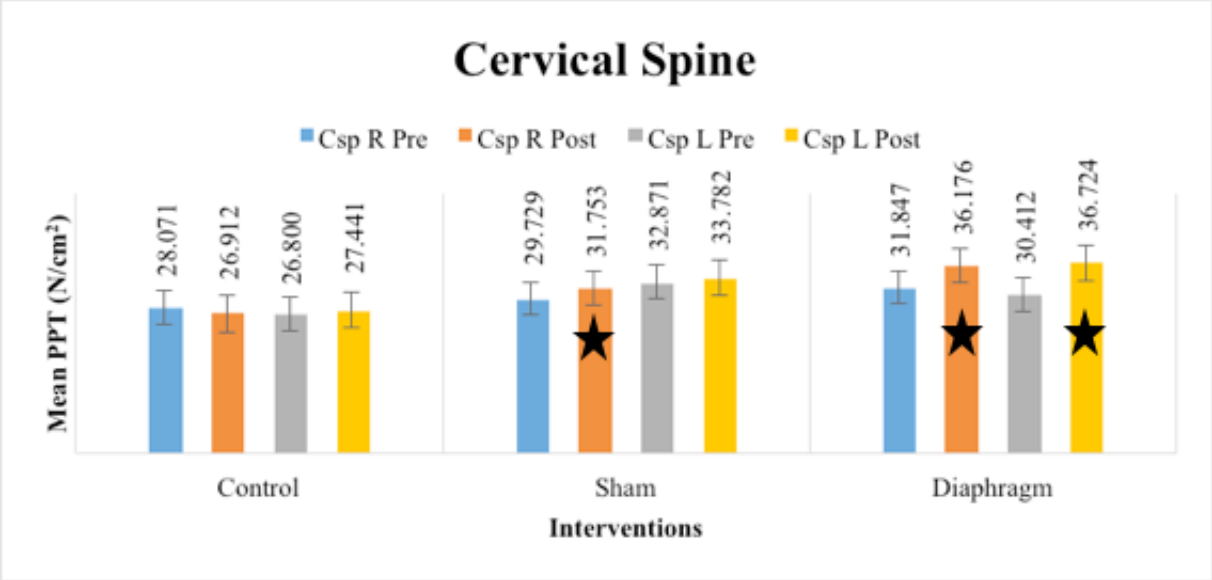

Figure 3: Shows mean PPT values for both pre- and post-intervention measurement in both sides of the cervical spine for all three intervention groups. Data are reported as mean ±SE, N=17. Bars with a star indicate statistically significant differences between pre- and post-intervention using paired samples *t*-tests ($p<0.05$). For the *t*-tests, these are calculated using actual pre- and post-intervention PPT scores within each intervention. Mean PPT values are provided for illustrative purposes and were not used during the statistical analysis.

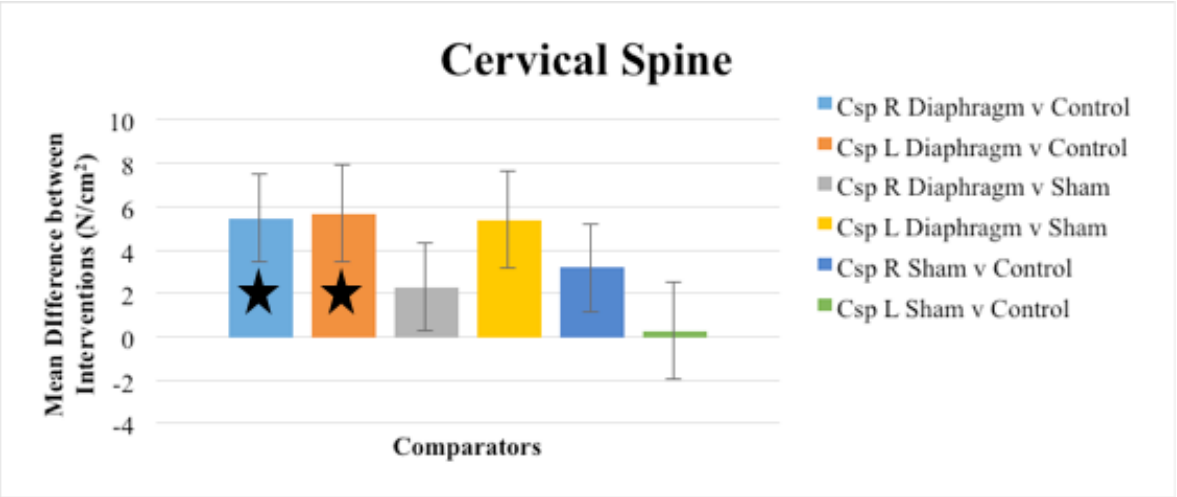

Figure 4: Shows the post-hoc mean differences from the one-way ANOVA, comparing the change in PPT values post-intervention for the cervical spine between intervention groups, at each side. Data are reported as mean, ±SE, N=17. Bars with a star indicate statistically significant differences between two interventions at the same side ($p<0.05$). Mean differences are shown for illustrative purposes only (actual pre minus post PPT scores are used for the intervention comparisons within the one-way ANOVA) and were calculated from the post hoc test of the one-way ANOVA which used the change of PPT values post-intervention as the single dependent variable.

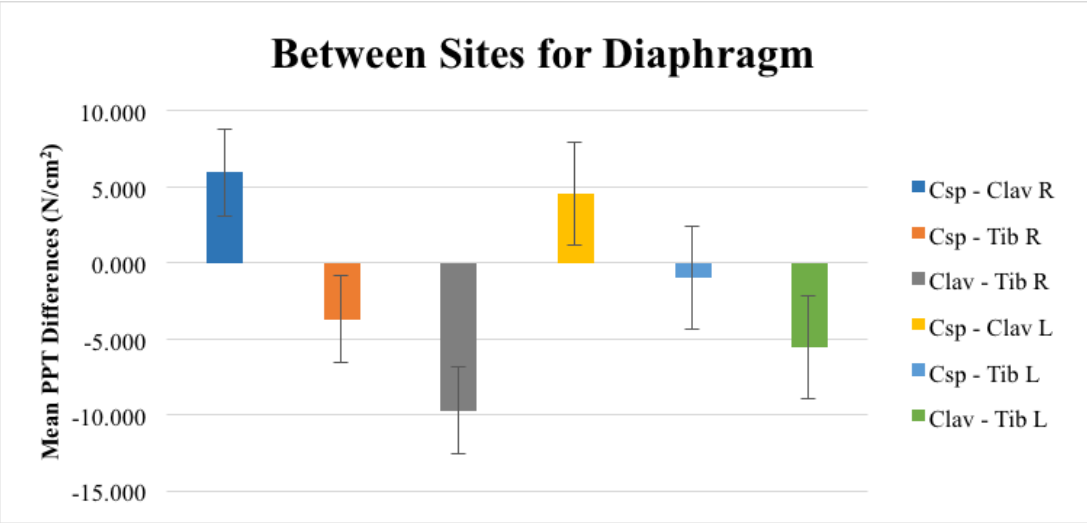

Figure 5: Shows the post-hoc mean differences from the one-way ANOVA comparing the change in PPT values between each site after the 'Diaphragm Release', at each side. Data are reported as mean, ±SE, N=17. Bars with a star indicate statistically significant differences between two sites of the same side immediately after the 'Diaphragm Release' ($p<0.05$). Mean differences are shown for illustrative purposes only (actual pre minus post PPT difference scores are used for the site location within the one-way ANOVA) and were calculated from the post hoc test of the one-way ANOVA which used the change of PPT values post-intervention as the single dependent variable.

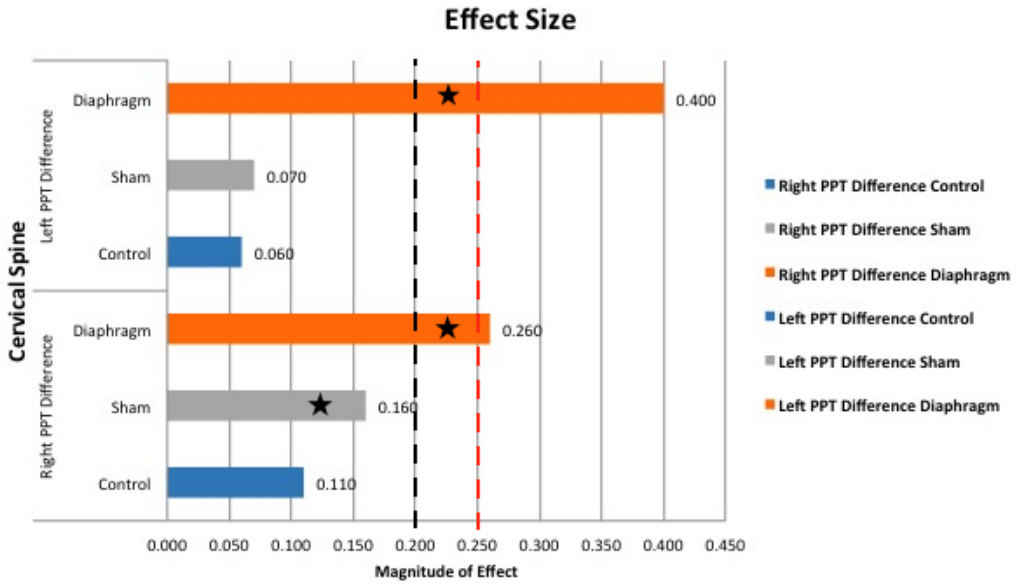

Figure 6: Shows the magnitude of the hypoalgesic effect in the cervical spine after all experimental conditions. Bars with a star indicate a statistically significant hypoalgesic effect ($p<0.05$). Black dotted line indicates a small effect size, $d= 0.2$ (Cohen, 1988), Red dotted line indicates an educationally significant effect, $d= 0.25$ (Wolf, 1986).

DISCUSSION

This study provides preliminary evidence of Regional Inhibitory Interdependence within a neurophysiological mechanism of pain modulation. Confirming that MT directed to a distal somatic structure can specifically induce an immediate hypoalgesic effect at the spinal segment of innervation. This statistically significant hypoalgesic effect, immediately following a 'Diaphragm Release' was observed in the cervical spine ($p< 0.02$) but not in the shoulder or distal site. This study demonstrated that performing a commonly used Osteopathic technique, 'Diaphragm Release', can produce a statistically significant hypoalgesic effect specifically in the right ($F(2,48) = 3.67$, $p= 0.034$) and left ($F(2,48) = 4.120$, $p= 0.048$) cervical spine when compared to no treatment. Although MT techniques have demonstrated segmentally specific hypoalgesic effects (McSweeney et al 2012; Paungmali & O'Leary 2003; Vicenzino et al 2001; Wright 1995), this is the first sham-controlled study to demonstrate and quantify the magnitude of a hypoalgesic effect on mean pain pressure thresholds in the cervical spine immediately following an Osteopathic technique. Effect size should be reported in addition to probability values as in research '*statistical significance is not sufficiently useful to be invoked as the sole criterion for evaluating the noteworthiness…*' (Thompson 2002 p. 66). The findings of a small and educationally significant hypoalgesic effect was shown in both the right (d =0.260) and left (d= 0.400) cervical spine sites after a 'Diaphragm Release' adds to the current literature by evaluating the magnitude of effect, in addition to the probability values. Although a direct comparison cannot strictly be established, the effect sizes in this research were similar to the hypoalgesic effect achieved using 1g of paracetamol compared to placebo in healthy subjects PPT measurements of both the finger and shoulder, d= 0.47 and d= 0.15, respectively (Meeus et al 2013). Averaging the percentage change between the right and left sides in the cervical spine (acceptable as there was no statistical difference between sides) demonstrates a 17.17% increase in mean PPT immediately after the 'Diaphragm Release'. This surpasses the minimum percentage change that indicates clinical significance as established by Moss et al (2007), a standard supported by (Krouwel et al 2010; McSweeney et al 2012; Voogt et al 2014). However, this figure was established upon symptomatic subjects and peripheral joint mobilisation. A wider range of mean PPT percentage change, 11% to 19%, has been observed in the literature investigating spinal mobilisations and visceral mobilisation in asymptomatic populations (Krouwel et al 2010; McSweeney et al 2012; Willett et al 2010). Pentelka et al (2012) demonstrated a higher increase in mean PPT that after 5 sets of mobilisation from 32-56%. Interestingly, studies utilising symptomatic participants with neck pain achieved much higher changes, 45% (Vernon et al 1990). This suggests that using a symptomatic population and increasing the dose would result in a greater percentage change and observing the small yet educationally

significant effect, this provides a solid foundation for further research into the clinical applicability of Regional Inhibitory Interdependance.

Although the hypoalgesic effect on the right side of the cervical spine reached statistical significance, $t(16)= -2.34$, p= 0.033, 95% CI (-3.86, -0.19) equivalent to a change of 6.81% after the sham intervention, some authors believe '*the primary product of a research inquiry is one or more measures of effect size, not P values*' (Cohen 1990 p. 12). The effect sizes after the sham intervention in the cervical spine, d = 0.16, was below that which is considered small and is classified as showing no effect (Cohen 1988). Nonetheless, contextual effects could explain the statistically significant hypoalgesic effect. The contextual in question is the non-specific effects of the theurapeutic encounter from therapeutic touch, practitioner interaction, patient expectation and beliefs (Bronfort et al 2010; Hartman 2009; Kaptchuk et al 2008; Quintner et al 2014).

The analgesic effects of touch has been quantified by Mancini et al (2014); their experiments demonstrated how tactile stimulation lasting only 1.5 seconds resulted in reduced pain perception. This phenomenon is supported both recently (Inui et al 2006; Nahra & Plaghki 2003) and in earlier works (Kakigi & Watanabe 1996). Even the effect of a warm stimuli applied to a part of the body, such as the hand, has shown to activate the rostal anterior cingulate cortex, which is known to correlate with pleasant touch and emotions (Rolls et al 2008; Rolls et al 2003). These studies help explain how prolonged skin-skin contact, as performed in the sham, can alter pain perception and create a significant hypoalgesic effect.

Both practitioner interaction and patient expectation are known to not only have a large influence in placebo analgesia, but have also been demonstrated to influence pain outcomes in MT intervention research. The placebo effect is considered a learned phenomenon whereby a participant learns to produce a beneficial effect from verbally induced expectations, cued and contextual conditioning, or social learning (Colloca & Benedetti 2009; Colloca et al 2013). It has been shown that patient beliefs and expectations enhance the hypoalgesic effect in various MT interventions, including those observed in subjects with neck pain (Bishop et al 2011; Bishop et al 2013; Kaptchuk 2002; Linde et al 2007). In the post-experimental questionnaire no participants were aware the sham was a forceless technique mimicking a BLT; therefore the sham was successful. Despite continous strict adherence to procedure and script, contextual effects are a practically inescapable repercussions for both MT research and Osteopathy in a clinical scenario due to practitioner interaction. A combination of all three factors can explain how contextual effects may have generated a statistically significant hypoalgesic effect at the cervical spine after the sham intervention.

Findings in this study support previous literature demonstrating that mean PPT increases in a caudal direction (Fischer 1987; Keating et al 2001; Potter et al 2006; Vanderweeen et al 1996). Both the cervical spine and clavicle sites add support to the findings by Fischer (1987) and Vanderweeen et al (1996), as no statistical differences were identified between the right and left sides pre-intervention in the cervical spine and clavicle in the control, sham and diaphragm interventions. Additionally, an excellent level of ICC reliability was calculated between both sides of the cervical spine, clavicle and tibialis anterior, as seen in Table 2.

This study supports the existence of Regional Inhibitory Interdependence, where directing treatment to distal somatic tissue can cause segmentally specific hypoalgesia. The osteopathic concept of *descending inhibition* where, for example, diaphramatic dysfunction can be alleviated by directing treatment towards the cervical spine, specifically C3-5 via is extensively discussed by Chila (2010), DiGiovanna et al (2005), and Sammut & Searle-barnes (1998). This study supports a reciprocal relationship utilising a concept, Regional Inhibitory Interdependence, to alleviate cervical spine pain, specifically C4, by directing treatment to the diaphragm. Furthermore, this study demonstrates strong methology as the chosen design removes between patient variables (Yang & Stufken 2008) and reduces the sample size required to that in a parallel study by up to 90% (Louis et al 1984), therefore it utilised resources economically (Yang & Stufken 2008). Additionally, this study suffered no drop outs, which can result in major methodological issues for a cross-over design (Mills et al 2009).

The small sample size (N=17) damages the generalizability of the results and increases the risk of both type I and II errors. Although a larger sample size would increase the power of the study and the chance of finding a significant difference, the number of participants in this study is larger than some previous studies investigating the hypoalgesic effect of MT (McSweeney et al 2012; Vicenzino et al 1996). Although this study supports the use of pressure algometry in MT research, there are known methodological flaws with the use of algometry (Antonaci et al 1998; Kosek et al 1993; Vanderweeen et al 1996; Vaughan et al 2007). One factor that may have affected the results is the steady rate of application (Nussbaum & Downes 1998). In future, to further eliminate this interference, computer software could provide feedback to the researcher to inform them on the rate of application and providing an electronic switch to the participants. Without time restrictions, a longer 'wash-out' period could have been implemented and a follow up measurement could assess the duration of significant hypoalgesia in the cervical spine.

CONCLUSION

The results of this study indicated a 'Diaphragm Release' immediately induced a clinically and educationally significant hypoalgesic effect in the cervical spine but not in the shoulder or distal site. This study supports a neurophysiological mechanism behind the effectiveness of manual therapy utilizing the concept of Regional Inhibitory Interdependence, however, the clinical applicability is undefined. Further research can elucidate this and investigate the permanency of the observed effect using a larger population, symptomatic patients and follow up measurements. This research supports a hypothesis that treatment to distal somatic tissue has both an effect locally and at the spinal segment of neurological supply, providing an incentive for future research into osteopathic concepts and other examples of Regional Inhibitory Interdependence.

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CONFLICTS OF INTEREST

Conflicts of interest: none

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Tables

	Age	Height (cm)	Weight (Kg)	BMI
Male	Mean = 21.2	Mean = 173.6	Mean = 80.7	Mean = 26.8
N = 5	SD = 1.3	SD = 5	SD = 12.1	SD = 4.2
	Range = 19-22	Range = 170 - 182	Range = 67-90	Range = 23.1 - 32.7
Female	Mean = 20.4	Mean = 165	Mean = 64.6	Mean = 23.8
N = 12	SD = 1.6	SD = 7.4	SD = 8.6	SD = 2.9
	Range = 19 - 24	Range = 152 - 178	Range = 55-82.7	Range = 19.9 - 30.6

Table 1 Demographic Data

Table 1 (SD = Standard Deviation, N = Number, BMI = Body Mass Index, Kg = Kilograms, cm = centimetres).

		95% Confidence Interval		
	Mean ICC	Lower Bound	Upper Bound	Level of Reliability
Csp R	0.870	0.707	0.949	Excellent
Csp L	0.901	0.777	0.961	Excellent
Between Csp	0.939	0.879	0.975	Excellent
Clav R	0.630	0.168	0.855	Good
Clav L	0.637	0.183	0.858	Good
Between Clav	0.844	0.692	0.935	Excellent
Tib R	0.755	0.449	0.904	Excellent
Tib L	0.851	0.664	0.942	Excellent
Between Tib	0.910	0.823	0.963	Excellent

Table 2 Intra-Rater Reliability

Table 2 (Csp= Cervical Spine; Clav= Clavicle; Tib= Tibialis Anterior).