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Title

A randomised, independent groups study investigating the sympathetic nervous system responses to two manual therapy treatments in patients with LBP.

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1. INTRODUCTION

The use of manual therapy (MT) techniques in the management of non-specific low back pain (LBP) has been advocated by a number of 'groups' including the National Institute for Clinical Excellence (NICE, 2009), the Chartered Society of Physiotherapy (CSP, 2006) and the Clinical Standards Advisory Group (CSAG, 2004). The term MT includes a myriad of techniques that focus on restoration of segmental motion with associated alleviation of symptoms (eg pain) and improvements in function. Foster et al (1999) and Poitras et al (2005) reviewed strategies utilised by physiotherapists for LBP patients. Of the approaches studied, segmental mobilisations/manipulations were favoured by 87% of respondents with reports of 47% utilising the 'McKenzie' approach. The publication of 'guidelines for the management of LBP' recommends the use of MT and exercise for the condition (CSP, 2006; van Tulder et al 2006; Savigny et al, 2009 and Chou et al, 2009). Furthermore, these guidelines are supported by studies demonstrating clear patient-reported benefits (Goodsell et al, 2000, Bialosky et al 2009b and van Middelkoop et al., 2011). However, there continues to be debate within the literature regarding how best to quantify effects and how to determine the magnitude and the clinical significance of observed treatment responses (Potter et al 2005; Theodore, 2010). Additionally, there is limited knowledge regarding the transferability of findings from

normative (asymptomatic) studies to patients with LBP and compromised function.

A limited number of studies have investigated and quantified the neurophysiological responses of selected MT techniques in the lumbar region (Perry and Green, 2008; Perry et al 2011, Moutzouri et al, 2012 and Tsirakis and Perry, 2015) with results in normative healthy populations reporting sympatho-excitatory responses to treatment. The magnitude of treatment effects regarding sympathetic nervous system (SNS) responses (as measured by skin conductance – SC) to lumbar MT techniques have previously been documented as a 76% increase (from baseline levels) for a rotatory manipulation (high velocity low amplitude thrust – HVLAT) and 36% for a repeated McKenzie extension in lying (EIL) technique (Perry et al., 2011). Other normative studies of MT techniques in the lumbar region have recorded similar increases in SC activity in the order of 30% for a 'spinal mobilisation with leg movement' technique (Tsirakis and Perry, 2015), 11% for a centrally applied sustained natural apophyseal glide to L4 (Moutzouri et al 2012) and 13 % for a unilateral posterior-anterior mobilisation (Perry and Green 2008). Furthermore, there is general agreement, within the literature, that changes in activity in the SNS are linked to central processing of pain and the instigation of hypoalgesia (Bialosky et al., 2009a). Many authors have postulated that an area of the mid brain, the dorsal peri-acqueductal grey area (dPAG), is, in part, instrumental in evoking this mechanism (Lovick, 1991; Lanotte et al., 2005; Potter et al., 2005 and Bialosky et al., 2009a). This construct is further supported by reports of

diminished pressure pain thresholds following different forms of MT with concurrent sympatho-excitation (Vicenzino et al., 1995; Sterling et al., 2001; Cleland et al., 2002; Cleland and McRae., 2002; Paugmali et al., 2003) and associated rises in levels of substance P (Molina-Ortega (et al., 2014). However, to date, there have been no clinical studies investigating whether SNS findings from normative studies reflects those from patients with LBP.

The primary aim of this translational study was to observe, in a clinical population with LBP, the immediate neurophysiological responses to two therapist-advocated treatments utilised in the physiotherapy management of LBP of up to 12 weeks duration. The two treatments; a segmental lumbar manipulation (HVLAT) technique (Maitland et al., 2001) and a repeated extension in prone lying exercise (EIL) (McKenzie 2003) have been previous investigated with respect to SNS responses (Perry et al., 2011) and the standardised treatment techniques, the operational protocol and the methods of data collection utilised were replicated within this study.

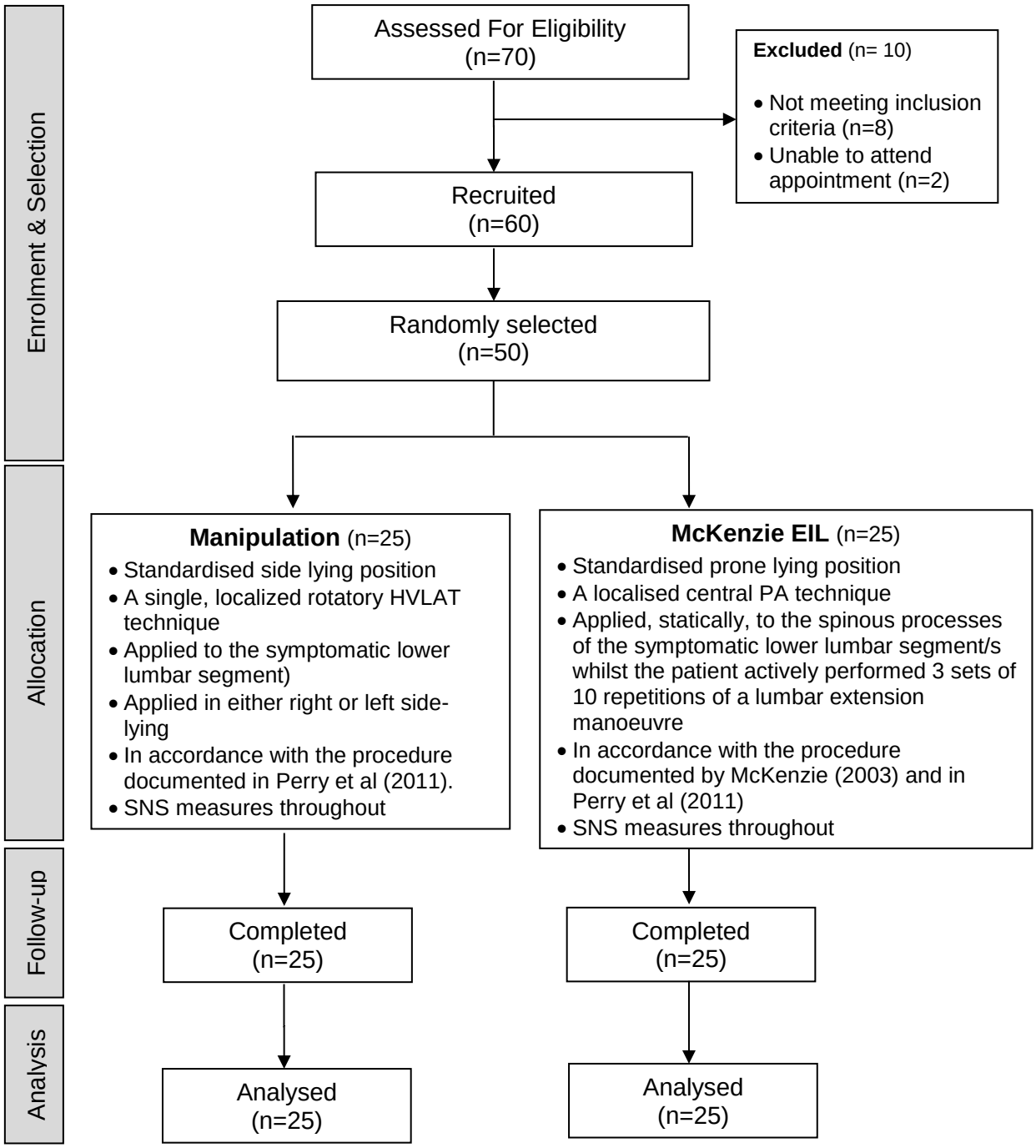
2. METHOD

A randomized, independent group's study design was utilized where participants were randomly selected from a larger patient cohort study that investigated the neurophysiological and patient-reported responses to a longitudinal course of guideline-endorsed physiotherapy treatment/s.

2.1. Participant selection, randomisation and cohort characteristics

Fifty patients with a history of LBP of less than 12 weeks duration were randomly selected (using a random numbers table constructed in the n-Query software package) by an independent statistician (blind to the study aims), from a larger patient cohort (n=60). These 50 participants were then randomly allocated (by a computer generated random numbers table in the above software package) into either one of two data extraction groups; HVLAT or EIL techniques for data comparison purposes. All patients had received both treatment components (in a computer-generated random order, to minimise order effects) however, only the data relating to the specific treatment was utilised for the analysis. Patients were recruited from the physiotherapy department at the University Hospitals of Leicester NHS Trust during the period July 2009 through to September 2011 (see Figure 1). All participants received information sheets about the study and gave informed consent prior to data collection. Ethical approval was gained from Coventry University Ethics Committee, NREC (Ref: 09/H0402/55) and the UHL NHS Trust R&D office (Ref: UHL10755).

Figure 1:
Consolidated Standards of Reporting Trials (CONSORT) flow chart of study participant enrolment, treatment allocation and analysis.



Inclusion criteria consisted of the following; non-smokers, aged between 18 and 55 years old with an onset of LBP within the previous 12 weeks, baseline narrative pain rating scale (NPRS) scores between 3-8 (out of 10) and Oswestry disability index (ODI) scores between 20-70% in an attempt to facilitate generalisability to the larger population and to homogenise the cohort. Exclusion criteria included flags of serious pathology, pregnancy, previous lumbar surgery, stenosis, instability, history of cancer or other serious pathology. Patients were also excluded if they had received previous physiotherapy/manual treatment of LBP or any absolute contraindications to manual or manipulative treatment (osteoporosis, prolonged use of steroids etc). Positive nerve root signs or sensory or motor deficit in the lower limbs were also excluded as were conditions that could affect SNS activity (psycho-pharmaceuticals, diabetes etc) or recordings of SC data (eg skin conditions affecting the feet). Details of the final cohorts are provided in table 1.

Table 1: Demographic characteristics by cohort

Characteristics	**Manipulation** (n-25)	**EIL** (n=25)	***p* value**
Sex (Male)	48%	44%	0.777
Age (mean in years)	41.7	38.7	0.734
Race (white Caucasian)	96%	96%	1.000
Duration of symptoms (in weeks)	6.6	8.3	0.802
Employment status Working full-time Working part-time Sick leave Other (not working)	 20% 24% 48% 8%	 28% 16% 40% 16%	0.664
ODI score (0-100%)	43.2	37.8	0.478
NPRS (0-10)	7.1	6.9	0.434

Pearsons Chi-squared tests of all variables did not reveal any significant differences between the 2 groups. The t-test was used to analyse age and ODI where no significant differences between groups were observed.

2.2. SNS outcome measures and study procedures

Physiological recording of SC was continuously measured, without interruption, throughout the entire experimental period by a Biopac MP35 Electro-dermal Activity Amplifier (Biopac Systems Inc; Santa Barbara, CA), employing a constant voltage technique and sampling the absolute, direct current SC at the rate of 200 samples per second using silver/silver chloride electrodes. The data analysis focused on the immediate effects of the specified treatments, within a single treatment episode.

Prior to data collection the skin of the 2nd and 3rd toes was prepared in accordance with standard protocol for Biopac measurement (Perry and Green, 2008; Perry et al., 2011). During the 10 minute stabilisation and following 2 minute ***baseline*** data collection periods participants lay supine upon an adjustable treatment plinth and were instructed not to sleep, deep breathe, cough or sneeze, talk, fidget with the sensors, or move unless otherwise instructed to do so by the investigator. Following previously documented protocols (Perry and Green, 2008; Perry et al., 2011), the treatment conditions were applied (***intervention period***) and the responses to the techniques identified (selected, in this study, retrospectively by the independent, assessor/statistician who was blind to the coded treatment allocation) for comparison with the baseline period (2 minutes of data were utilised within the treatment period). After completion of the treatment period, 10 minutes of rest were provided and the final 2 minutes of this period recorded (***final rest period*****)** for comparison to the baseline and treatment periods. By turning the laptop screen away from the treatment area neither the participant nor the treating therapist were able to receive any feedback regarding SNS activity, thus ensuring the blinding of the participant and the therapist to the responses to the treatment. The same therapist conducted all treatments in accordance with the protocol provided in the Perry et al. (2014) study. At the start of the study the treating therapist had been qualified 22 years and had completed an MSc in Manipulative Therapy.

Manipulation (HVLAT) Technique: - A single, localised (high-velocity low amplitude grade V manipulation) segmental rotation technique (applied to the symptomatic lower lumbar segment) in either right or left side-lying according to the detailed protocol described in Maitland et al (2005), by Herzog (2000) and in accordance with the procedure documented in Perry et al (2011).

EIL Technique: - A localised central postero-anterior technique statically applied to the spinous processes of the symptomatic lower lumbar segment/s whilst the patient actively performed 3 sets of 10 repetitions of a lumbar extension manoeuvre in prone lying according to the protocol described by McKenzie (2003) and utilised in the study of Perry et al (2011).

2.3. Sample size calculation

As SC changes (from baseline to treatment intervention) were the primary outcome measure of the study, data from previous SC literature was used to determine the sample size. Perry and Green (2008) recorded SC values in the lower limbs in control, placebo and lumbar treatment situations. Using the n-Query advisor software package, and based upon a pooled standard deviation estimate from placebo and control groups of 9.4%, it was calculated that 50 patient participants (25 per group) would enable a SC value difference of 7.5% in percentage change from baseline to be detected at the 5% significance level with 80% power. This effect size was selected as it has been utilised in a previous paper looking at SNS treatment responses to lumbar mobilisations (Perry and Green, 2008) and was greater than the reported Smallest Real

Difference (SRD) value of 4.63% (0.315µMho's), a value above which any SC responses can be considered to be a result of the intervention under investigation rather than that of measurement error (Perry et al., 2011).

2.4. Data Analysis of skin Conductance

The Predictive Analysis Soft Ware package (PASW v.20) was used for all analyses. Baseline characteristics were compared between the two groups using Chi-squared tests for categorical data (sex) and ordinal level (NPRS) variables. Student t-tests were used to compare continuous variables (age and ODI scores) between the 2 treatment cohorts.

Analysis of the primary SC data obtained involved calculation of the "Integral Measurement" (µMho's) for *baseline, treatment* and *final rest periods*. *Treatment* and *final rest period* values were also converted into percentage change (PC) from baseline using the formula detailed in a previous paper (Perry and Green, 2008) to allow between participant comparisons. Paired t-tests were used to explore within-group responses to treatment from baseline and into the final rest periods. Independent t-tests were employed for between-group comparisons of treatment effect. The level of significance was set at 95% ($p<0.05$).

3. RESULTS

3.1. Cohort characteristics comparability

Comparisons of the demographic characteristics of both cohorts were performed, and the results summarized in Table 1. The 2 treatment groups did not differ significantly on any of the variables including measures of pain intensity (NPRS) and perceived disability (ODI).

3.2. Skin Conductance Analysis

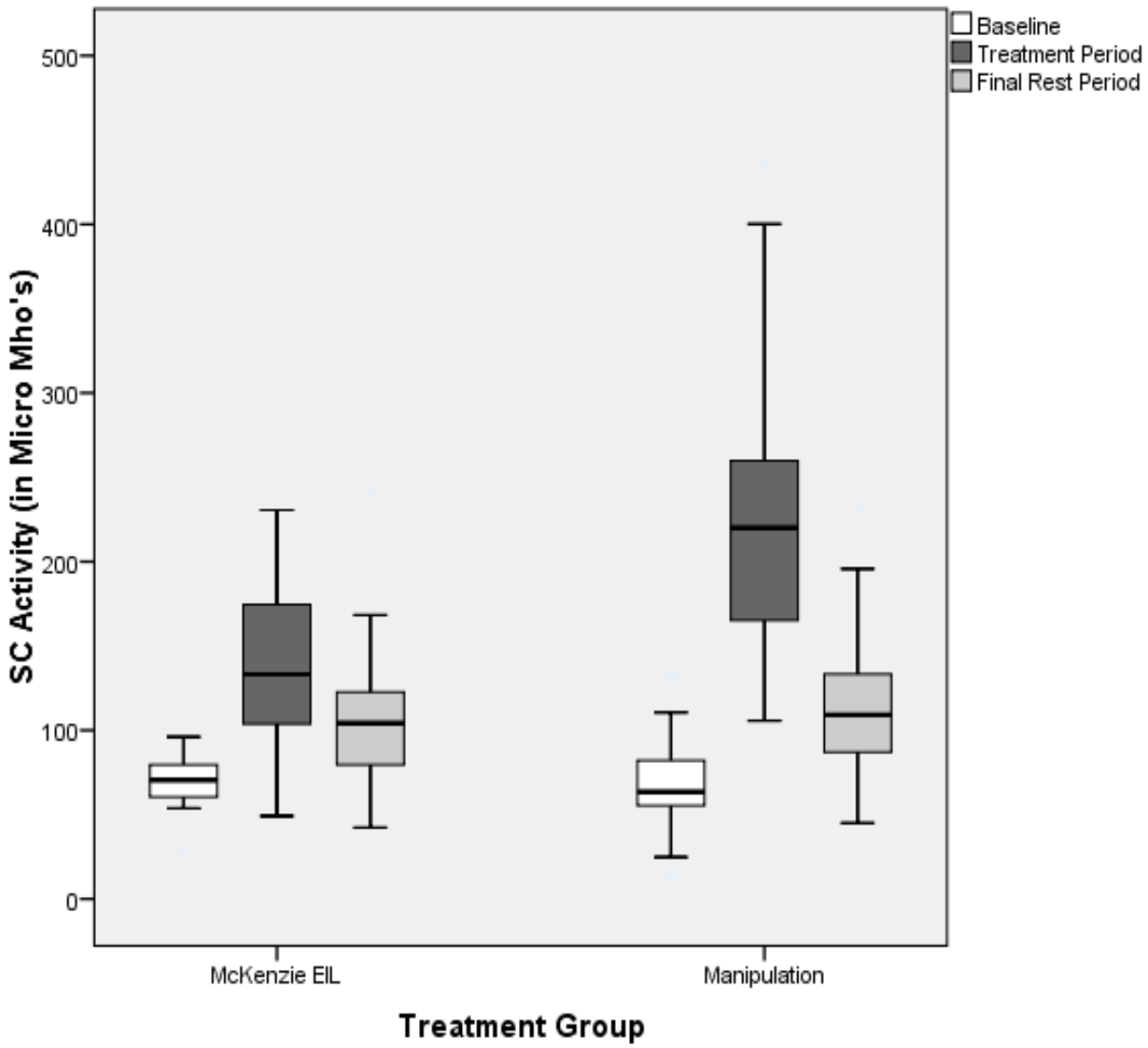
The primary outcome measure in this study was skin conductance. Analyses consisted of; comparisons of SC activity levels (in µMho's) at the 3 different time periods, and percentage change (PC) in SC from baseline to treatment, baseline to final rest period and treatment to final rest period. Results are presented in Table 2 and illustrated in Figure 2.

Table 2: The skin conductance (SC) Activity levels (µMho's) **and percentage change values (SCR) in response to the two treatment techniques.**

Skin Conductance	**HVLAT Manipulation Group** (n=25)	**McKenzie Repeated EIL Group** (n=25)	**Between Group Comparisons** *(p value)*
SC activity (µMho's)			
Baseline	68.3 (+/-29)	70.2 (+/-15)	0.765
Treatment Period	223.5 (+/-88)†	137.9 (+/-50)†	<0.005*
Final Rest Period	115.7 (+/-49)†‡	110.2 (+/-43)†‡	0.675
Mean percentage change - Baseline to Treatment Period (SD) *(CI 95%)*	255% (+/-141) *(CI 177 to 323)*	94% (+/-44) *(CI 80 to 129)*	<0.005*
Mean percentage change - Baseline to Final Rest Period (SD) (*CI 95%)*	85 (+/-81) *(CI 62 to 101)*	63 (+/-72) *(CI 39 to 87)*	0.312
Mean percentage change - Treatment Period to Final Rest Period (SD) *(CI 95%)*	-47 (+/-16) *(CI -29 to -62)*	-15 (+/-32) *(CI 5 to -29)*	<0.005*

Where: * indicates a significant difference between groups; † Indicating a significant within-group difference from baseline; ‡ indicating a significant within- group difference from treatment period (p<0.05).

Figure 2: Clustered box-plot of SC activity levels (in µMho's) of the 2 treatment groups during the 3 time periods.



The results indicate a sympatho-excitatory response to both treatment techniques (from baseline). Within-group comparisons highlighted a greater magnitude of response for the manipulation technique compared to the EIL technique. The manipulation technique increased SC activity levels, from baseline, by 255% (mean difference 155.2 µMho, t=11.935, p<0.005) and the EIL technique by 94% (mean difference 67.7 µMho, t=8.685, df 24, p<0.005). Furthermore, within-group analysis indicated that whilst there was a significant

drop in SC activity from treatment into the final rest period for both treatments (manipulation mean difference -107.8 µMho, t= -7.394, *p*<0.005; EIL mean difference -27.7 µMho, t= -2.518, *p*<0.019) both techniques significantly sustained their level of sympatho-excitatory response above baseline levels, into the final rest period (manipulation mean difference 47.4 µMho, t=6.722, *p*<0.005; EIL mean difference 40.0 µMho, t=4.488, *p*<0.005).

Between-group comparisons of SC activity levels across the different time periods revealed no difference during the baseline periods (pre-treatment mean difference 1.98 µMho's; p=0.765) supporting homogeneity of the groups pre-treatment. There were, however, significant differences between-groups during the treatment period with the manipulation technique having a greater magnitude of response compared to the EIL technique (mean difference 85.58 µMho's; p<0.005). There was no significant between-group difference in the final rest periods (mean difference 5.50 µMho's; p=0.675).

4. DISCUSSION

This study is the first to investigate neurophysiological/SNS (SC) responses to two commonly utilized treatment techniques within a clinical patient cohort presenting with LBP of less than 12 weeks duration. The findings indicate that SC responses to treatment can be recorded and quantified within patient populations and within a clinical environment rather than a laboratory setting. The two treatments both resulted in sympatho-excitation values that were

greater than the SRD value (0.315 μMho's or 4.632%) indicating that the observed responses were not due to measurement error/variability and were therefore ascribable to the interventions undertaken (Perry et al., 2011). Furthermore, the manipulation technique had the greatest magnitude of response (255%) compared to the EIL treatment (94%) which are comparable to the sympatho-excitatory findings reported in a operationally similar, normative study that also undertook lumbar rotatory manipulation (SCR of 76%) and EIL techniques (36%). Interestingly, despite both cohorts (symptomatic and asymptomatic) having similarities in the nature of the SC responses and in the differences in magnitude between the 2 techniques (almost three-fold), the patient participants in the present study had considerably larger SC responses to both treatments compared to the asymptomatic norms (manipulation techniques > 3 fold; EIL treatment > 2 fold).

The differences observed between the findings of this clinical cohort and those reported in the comparable normative study (Perry et al., 2011) may be explained by a number of factors; the environment (clinical versus laboratory), the therapeutic application of the 2 techniques and/or the nature of the participant (pain and functionally limited patients versus asymptomatic healthy norms). Considering these in turn; regarding the environmental factors it may be argued that a busy hospital out-patients clinic (with uncontrolled noise, temperature and humidity) could not be farther from the controlled, quiet environment of a laboratory. However, previous research conducted in an uncontrolled, non-laboratory setting reported SRD values (a percentage change

in SC > 4.63%) as being a meaningful change beyond that considered to be due to measurement error or external or systematic influence (Perry et al., 2011). Thus, support exists for the comparative differences between the patient and asymptomatic populations (in the order of 179% for the manipulation technique and 58% for the EIL treatment) indicating that results were unlikely to be solely due to environmental anomalies. The possibilities that observed SC differences between the symptomatic and asymptomatic populations were due to differences in the application of the two treatments were considered. Negating this argument was the replication of the protocol and treatment procedures in the normative study reported by Perry et al (2011) including hand positions and treatment timings. The most likely explanation for the greater magnitude of SC response in the patient cohorts was considered to be nature of the differences in the presentation of the symptomatic participants (who reported with pain and functional limitation) compared to the asymptomatic participants in the Perry et al (2011) study. Supporting this construct, a number of researchers have described the presence of enhanced/"up-regulated" dorsal horn (DH) neuronal excitability in patients experiencing back pain and symptoms (Bakkum, 2007; Boal and Gillette, 2004; Woolf, 2004 and 2011), a phenomenon not evident in asymptomatic populations. Furthermore, adaptive neuroplastic changes to the DH and CNS have been reported in response to lumbar dysfunction (Boal and Gillette, 2004; Taylor and Murphy, 2010) and been specifically correlated to pain activated regions in the brain, specifically; the Thalamus, Amagdala and Brainstem (Piché, Arsenault and Rainville, 2010; and Nagai et al., 2004) and to the peri-aqueductal grey (PAG) region as well as

to the descending pain inhibitory system (DPIS). The later are generally associated with changes seen in SNS activity levels (Lovick, 1991; Nagai et al, 2004 and Janig, 2013). To corroborate this theory, further research is recommended that correlates longitudinal SC responses to treatments with changes in patients pain reports and/or functional disability scores from treatment inception to discharge.

Few SNS and SC activity studies have been performed on patient populations and none published that have looked at the lumbar spine and lower limbs. Other studies that have recruited patients have explored the thoracic and cervical regions but have reported effects of lesser magnitude (16%, Sterling et al., 2001) possibly reflecting regional differences in peripheral cutaneous innervation or central processing systems. Schmid et al., (2008) conducted a systematic review of 15 papers that explored the evidence for a CNS component to the responses observed with passive mobilizations in the cervical spine. In their pooled data analysis Schmid et al., (2008) reported SC responses (mean pooled differences between intervention and control measures) of 35.1% (+/- 16.5), however, these results did not distinguish between the data gathered from asymptomatic norms and from patient participants, indeed, of the studies meeting the quality criteria for the review, only 7 reported SC findings, and of those, only 2 included patient populations that lacked normative comparisons (Vicenzino et al. 1998 and Sterling et al., 2001). Nonetheless, the findings here would support the concept that patients (with LBP of up to 12 weeks duration) could be demonstrating heightened SNS responses that are indicative of an adapting neurological pain

processing mechanism and that the responses seen in asymptomatic participants are not analogous with normative participant.

Of note, patients in this study underwent a “therapeutic” treatment experience comprising of a number of strategies, in accordance with CSP and NICE guidelines on LBP management (eg. MT, exercise, education about their symptoms and advice on self-management, return to work and staying active). Tracey et al. (2002) found that there was a distinct correlation between the level of engagement of the DPIS, pain reports and levels of ‘distraction’ (including placebo and expectation) and Wagner et al. (2004) found that the PAG and dorso-lateral prefrontal cortex (emotions centre) can be selectively activated during anticipation of an “event”, triggering opioid release within the brain-stem thus modulating pain perception. It is possible that instigation of a MT technique might constitute just such an “event” and be powerful enough to result in the cascade of central processing responses that may be responsible for clinically observed improvements. Whilst the authors attempted to limit the potential of confounding influences on the SNS (by adhering to a predetermined procedure) it was not possible to determine the effects of treatment “expectation” (Bialosky et al., 2008) and of “advice” on SNS activity and this might be considered a limitation of the study. Future studies are recommended that assess and correlate the expectations of the patient participants to the recorded magnitude of SNS responses.

The results reported should be interpreted with caution as no control or placebo conditions were incorporated into the design thereby limiting any direct cause and effect relationship. It does however provide some encouraging insight into the use of SC measures as a proxy indicator of neural excitability/sensitization in the presence of LBP.

6. CONCLUSION

This study, comparing SC response's to 2 commonly used physiotherapy treatments within a patient cohort provides evidence to support that both lumbar rotatory manipulation and McKenzie repeated EIL techniques result in a significant sympatho-excitatory response with the manipulation technique having over twice the magnitude of SNS effect as the EIL technique. Whilst these results are directionally similar to those of previously reported normative cohorts receiving the same treatments, this study challenges the assumption that symptomatic and asymptomatic populations are analogous. Results suggested that patients with LBP are more (SC) responsive to both treatments (almost three-fold) than their asymptomatic counterparts, suggesting that DH sensitization, in the patient group, may be a feasible explanation of the results and detectible by the proxy measurement of SC change. Future recommendations for research, in patient populations, are proposed to further elucidate these findings.

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