A Longitudinal Observational Clinical Study of Neurophysiological and Patient-Reported Responses to a Program of Physiotherapy for Acute and Subacute Low Back Pain

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Abstract

Objectives: The purpose of this study was to document the baseline neurophysiological status (skin conductance activity levels) of patients presenting for physiotherapy with acute and subacute low back pain (symptoms of up to 12 weeks' duration) and to observe the magnitude and direction of sympathetic nervous system (SNS) changes (skin conductance responses [SCRs]) occurring as a result of receiving guideline-endorsed physiotherapy treatment.

Methods: A pragmatic, prospective, longitudinal, observational study recording SNS skin conductance (SC) responses and patient reported outcome measure changes to a program of guideline-endorsed physiotherapy treatment for low back pain symptoms of up to 12 weeks' duration. Sixty patients received a guideline-endorsed physiotherapy treatment program. Continuous neurophysiological recordings of SC activity levels were taken throughout each treatment. Patient reported outcome measure data were extracted from inception, midpoint, and discharge. Within and between treatment analyses determined the nature of SC changes and correlations to longitudinal changes in pain and function. Skin conductance changes were measured within and between treatment episodes at treatment inception, midpoint, and discharge and observed correlations between the magnitude of SCRs, pain abatement (numeric pain rating scale), and functional restoration (Oswestry Disability Index).

Results: Skin conductance changes were significant during all "treatment" periods ($P = .044$), with the greatest magnitude of sympathoexcitatory responses occurring at inception (219%). The treatment modality providing the maximum SNS response was a high-velocity lumbar rotation manipulation. Positive correlations were identified between SCRs, Oswestry Disability Index improvements ($r = 0.82$, $P < .0005$), and pain abatement ($r = 0.459$, $P < .0005$).

Conclusions: Patients with low back pain exhibited neurophysiological treatment responses indicative of a symptom-related neuroplastic state of dorsal horn sensitization that may be receptive to early manual therapy intervention. (J Manipulative Physiol Ther 2018;41:456-466)

Key Indexing Terms: *Low Back Pain; Manipulation, Spinal; Patient Reported Outcome Measures; Sympathetic Nervous System*

Introduction

Despite 2 decades of published guidance supporting the use of physiotherapy in the rehabilitation of patients with low back pain (LBP), there continues to be a paucity of empirical knowledge that can support evidence-informed clinical decisions, guide patient choice, and advise policy makers. Indeed, clinical practice guidelines for the management of LBP[1] advocate the use of therapeutic techniques such as manual therapy (MT) and exercise therapies, although the specifics of the treatments remain under debate. Nonetheless, MT treatments are implemented by 73% of United Kingdom physiotherapists[2] and continue to be integral to multimodal packages of care. Research evidence has provided support

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for the use of MTs and exercise therapies on this patient group[2,3] with improvements, beyond the natural course of symptom resolution, being reported both subjectively; utilizing patient-reported outcome measures (PROMs) of pain intensity[4] (ie, numeric pain rating scale [NPRS]) and functional disability[5] (ie, Oswestry Disability Index [ODI]); and objectively or neurophysiologically utilizing immediate changes in measures of sympathetic nervous system (SNS) activity.[3] Adaptive changes in neurophysiological responses to guideline-endorsed treatments throughout a course of therapy have yet to be reported; furthermore, no previous study has described observed correlations between neurophysiological responses and traditional PROMs, which may provide preliminary clinical insight into the possible mechanisms of action of a number of therapeutic techniques utilized in this clinical cohort.

In 2009, Bialosky et al[6] described, in their model of the mechanisms of action of manual therapy for musculoskeletal pain, the links between changes in the measurements of SNS activity and observed pain modulatory responses at both spinal and central levels. Moreover, Perry et al[7] established that skin conductance (SC) measurements could be reliably recorded between data sessions (intraclass correlation coefficient = 0.99, $P < .005$) with a smallest real difference (SRD) value of 0.315 μmhos (a 4.633% change in SC readings), indicating that any SC change above the SRD could be regarded as an SNS response that is independent of any measurement error or variability, thus representing a real change ascribable to the intervention under investigation. Clinically, Perry et al[3,7] were the first to describe and compare immediate SNS responses, in both normative and symptomatic groups, to 2 lumbar treatment modalities (manipulation and McKenzie extension in lying exercises[8]). Interestingly, despite similarities in the direction of observed sympathoexcitatory SC responses (SCRs) to treatment, differences in the magnitude of the SNS responses were notable between asymptomatic and symptomatic participants with during-treatment SCRs for the clinical group being 3 times greater than those of healthy groups. This enhanced SCR in the symptomatic group has been suggested to represent an adapted "up-regulated" dorsal horn (DH) with resultant enhancement of neuronal excitability to therapeutic, mechanical stimulation.[9-12] To date, only immediate SNS responses to lumbar treatments have been reported, with none that have documented and compared PROMs with the longitudinal changes in neurophysiological activity levels within and, uniquely, between treatment episodes lasting for 4 to 8 weeks.

The aims of this study included documentation of the baseline neurophysiological status (skin conductance activity [SCA] levels) of patients presenting for physiotherapy with acute and subacute LBP (symptoms of up to 12 weeks' duration) and observation of the magnitude and direction of SNS changes (SCRs) occurring as a result of receiving guideline-endorsed physiotherapy treatment (a complex health care intervention) reporting results at 3 data capture points (at inception/commencement of treatment, at midpoint, and at discharge). The secondary aims of the study were to identify potential correlations in changes in SNS status and treatment SCRs to PROM and to identify any "active components" to the therapeutic encounter (notably, to describe the treatments that produced the greatest magnitude of SC response during each encounter).

Methods

A pragmatic, prospective, longitudinal, observational study design was selected to detect patient neurophysiological responses and PROM changes in response to a program of guideline-endorsed physiotherapy treatment.

Sample Size Calculation and Participant Recruitment

The number of participants required to detect a statistically significant difference ($P < .05$) at 80% power with an effect size of 0.38 (35% mean percentage change [PC] in SCR as a meaningful SCR difference from baseline for the treatment component; standard deviation 92%) was calculated to be 57 patient participants. Anticipating a drop-out rate of 10% to 20% (5-13 patients), up to 70 patients needed to be recruited for the study (Fig 1).

Ethical approval was obtained from the University Ethics Committees at Coventry University, the NHS Research Ethics Committee (NREC Ref: 09/H0402/55), and the University Hospitals of Leicester (UHL NHS Trust) Research and Development Office (Ref: UHL 10755).

Patient recruitment, assessment, and treatment took place between July 2009 and May 2011. Good retention of participants meant that during this period, a purposive and convenience sample of 60 patients with LBP was recruited at the physiotherapy department at the University Hospitals of Leicester NHS Trust (Fig 1). Informed consent was obtained from all patients in the study. They satisfied the study criteria (Fig 2) and were assessed as having a mechanical presentation of symptoms with restriction of 1 or more lumbopelvic movements and 1 or more hypomobile lumbar segments on palpation. Patients with red and yellow flags were excluded from the study to maintain cohort homogeneity.

The patients' inception demographic characteristics and PROMs are detailed in Table 1. Participants were informed (prior to attending their appointments) that they were required to avoid certain behaviors, such as consuming food, alcohol, or stimulants (eg, drinks with caffeine and nicotine products[13]) and to avoid heavy exercise 4 hours prior to appointments[14] because these factors are known to alter SNS activity. Participant compliance with these prohibitions was monitored by way of a series of screening questions prior to each treatment session. All participants were adherent to the protocol.

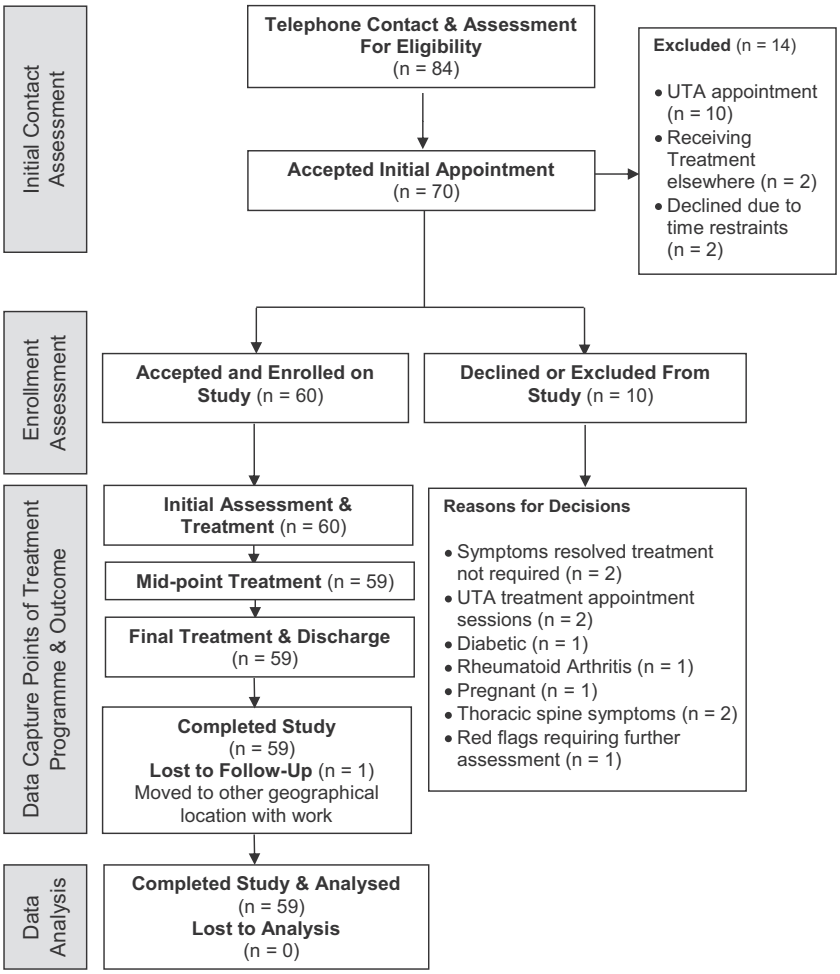

Fig 1. *Consolidated Standards of Reporting Trials flow chart of study participant enrollment, treatment allocation, and analysis.* UTA, *unable to attend.*

In accordance with data recording in other studies,[3,7,15] care was taken to not allow the patients to fall asleep, cough, sneeze, deep breathe, or talk while baseline SNS measurements were recorded. By obscuring the laptop screen from the treatment area, neither the patient nor the treating therapist was able to receive feedback regarding SNS activity, thus ensuring blinding of both participant and therapist to the effects of treatment.

Treatment programs were designed to be completed within a 6-week period, thus limiting the potential influence of external events (eg, changes in job) or habits (eg, taking up a new hobby or sport) and limiting the effects of natural regression to the mean. Participants attended, in accordance with the standard Trust procedure, until they reached a point in their symptom presentation at which they were considered fit for discharge (ie, reports of pain were intermittent and NPRS $\leq$1; restoration of pain-free range of lumbar motion; or at the patient's request after the patient had achieved personal goals [eg, return to work or desired functional activity level]).

Treatment interventions were composed of a patient and symptom-tailored program governed by the recommendations within the National Institute for Health and Clinical Excellence[16] guidelines, namely: advice (to remain active on pacing activities and on the benefits of return to work), education (about their symptoms and their condition), and specific exercise (ie, tailored McKenzie extension exercises,[8] core stability exercises, and trunk strengthening), in addition to a selection of all or some of the following: general exercise (cardiovascular aerobic exercises including the Trusts' back class) and MT (eg, facet joint and sacroiliac joint high-velocity low-amplitude thrust [HVLAT] manipulation, joint and soft tissue mobilizations, and mobilizations with movement techniques). During, and throughout, each therapy appointment (inception, midpoint, and discharge) SC measurements were recorded, and from each data record, 3 key 1-minute periods were subsequently identified and extracted (by a third party, blind to the nature of the treatments being undertaken) for comparative analysis purposes, namely the last minute of the

Inclusion Criteria

- Patients with an acute presentation of nonspecific LBP ≤ 12 weeks' duration
- Male and female sex
- Age between 18 and 55 years
- Possesses an adequate understanding of spoken English
- NPRS ≥ 3/10
- ODI baseline score of ≥ 14%
- Mechanical provocation of symptoms/pain: postures, movement and activities

Exclusion Criteria

- Sick-listed for more than 12 weeks
- Chronic exacerbation of LBP
- Existence of concurrent medical disorders or psychiatric illnesses that may affect neurophysiological readings (eg, diabetes, anxiety disorders, multiple sclerosis, rheumatoid arthritis)
- Patients with previous lumbar spine surgery or lower limb surgery
- Pregnancy
- Skin disorders at the site of electrode placement (eg, athlete's foot, psoriasis, eczema, verruca)
- Previous history of trauma with resultant persistent dysesthesia (chronic abnormality of sensation, which would affect neurophysiological readings)
- Alcohol dependency and smokers (could affect neurophysiological readings)
- Those with precautions and contraindications to physiotherapy treatment (including exercise classes)
- Those participants not willing or able to consent to inclusion

Fig 2. *Inclusion and exclusion criteria.* LBP, *low back pain;* NPRS, *numeric pain rating scale;* ODI, *Oswestry Disability Index.*

10-minute stabilization (baseline), 1 minute of the treatment time that represented the maximum response (max treatment), and the final minute of the post-treatment period (final rest) (Fig 3). Identification of the nature of the treatment intervention that produced the maximum response was documented for descriptive purposes only.

Skin Conductance Measurements and Data Management

Neurophysiological recordings of SC were continuously measured, without interruption, throughout each of the treatment episodes (up to 45 minutes) by a Biopac MP35 Electrodermal Activity Amplifier (Biopac Systems Inc, Santa Barbara, California), employing a constant voltage technique and sampling the absolute, direct current SC at the rate of 200 samples per second. Electrodes were placed on the second and third toes of both feet in accordance with the protocol described by Perry et al.[3,7]

After completion of all patients' treatment programs, retrospective calculations of the midpoint of their treatment course was established for each of the 59 participants completing the study (1 dropout was incurred due to geographical relocation). Most programs of treatment (including initial assessment) took between 3 to 5 sessions (maximum 8) and were in accordance with the normal Trust protocol. Patient reported outcome measures were completed at the start of each appointment.

Data Analysis of Skin Conductance

Analysis of the SC data obtained utilized the "integral measurement" (μmhos) function in the Biopac software. These were calculated for baseline, treatment, and final rest periods within each of the treatment episodes at each data capture point (inception, midpoint, and discharge). For each data capture point within (baseline, during treatment, and final rest period) and between each episode of treatment (inception, midpoint, and discharge), the results from both limbs were pooled (SCA levels) using the following calculation:

$$\text{Pooled SCA} = \frac{\text{Left leg SCA} + \text{Right leg SCA}}{2}$$

To facilitate between-participant data comparisons, SCA levels were converted into PC from baseline using the formula detailed in a previous paper.[15] This data was termed the SCR and was expressed as a percentage. Therefore, the maximum effect indicator could be expressed as either the SCA level (μmhos) or as SCR (PC) depending upon whether the focus of the analysis was within or between participant or event.

Prior to inferential testing (a repeated measures analysis of variance using generalized linear model), data distributions were checked for normality (skewness and kurtosis) and all statistical analyses were independently checked and verified by a statistician. Skin conductance response correlational analyses utilized Spearman rank (pain, NPRS) and Pearson's product moment (function, ODI) statistics. All P values were 2-sided tests, and the significance level for all analyses was set at 5% ($P < .05$) and run through SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, New York).

Results

Of the 60 participants who entered the study, 59 completed their course of treatment (Fig 1). All primary (SCA and SCR) and secondary (ODI, pain intensity/NPRS) data were collected (baseline, treatment and final rest periods at inception, midpoint, and at discharge) and formed the basis of the completed analyses (Table 2). The mean age of participants was 39 years, with 25 males and 35 females. At treatment inception, the mean symptom duration was 7 weeks with 65% either unable to work or on reduced hours due to their symptoms (Table 1). The PROMs, at inception, revealed that the average level of

Table 1. *Summary of the Key Patient Demographics and Outcome Measures at Initial Assessment*

n = 60			Mean (SD)	Minimum	Maximum	Standard Error
Age (y)			39.75 (8.3)	21	54	1.07
Sex (male)			42%	-	-	-
Race (white)			96%	-	-	-
Employment status						
Working full-time			16%	-	-	-
Working full-time (reduced hrs)			20%	-	-	-
Working part-time			19%	-	-	-
Working part-time (reduced hrs)			3%	-	-	-
Sick leave			40%	-	-	-
Other (not working)			2%	-	-	-
Symptom duration (w)			7.03 (3.6)	1	12	0.47
Primary outcome measure		Max SCR (%)	219.4 (153.1)	80	811	19.76
Secondary outcome measures	Fuctional disability	ODI (%)	42.93 (17.8)	16	86	2.30
	Pain intensity	NPRS	7.50 (1.4)	4	10	0.17

NPRS, numeric pain rating scale; *ODI*, Oswestry Disability Index; *SCR*, skin conductance response; *SD*, standard deviation.

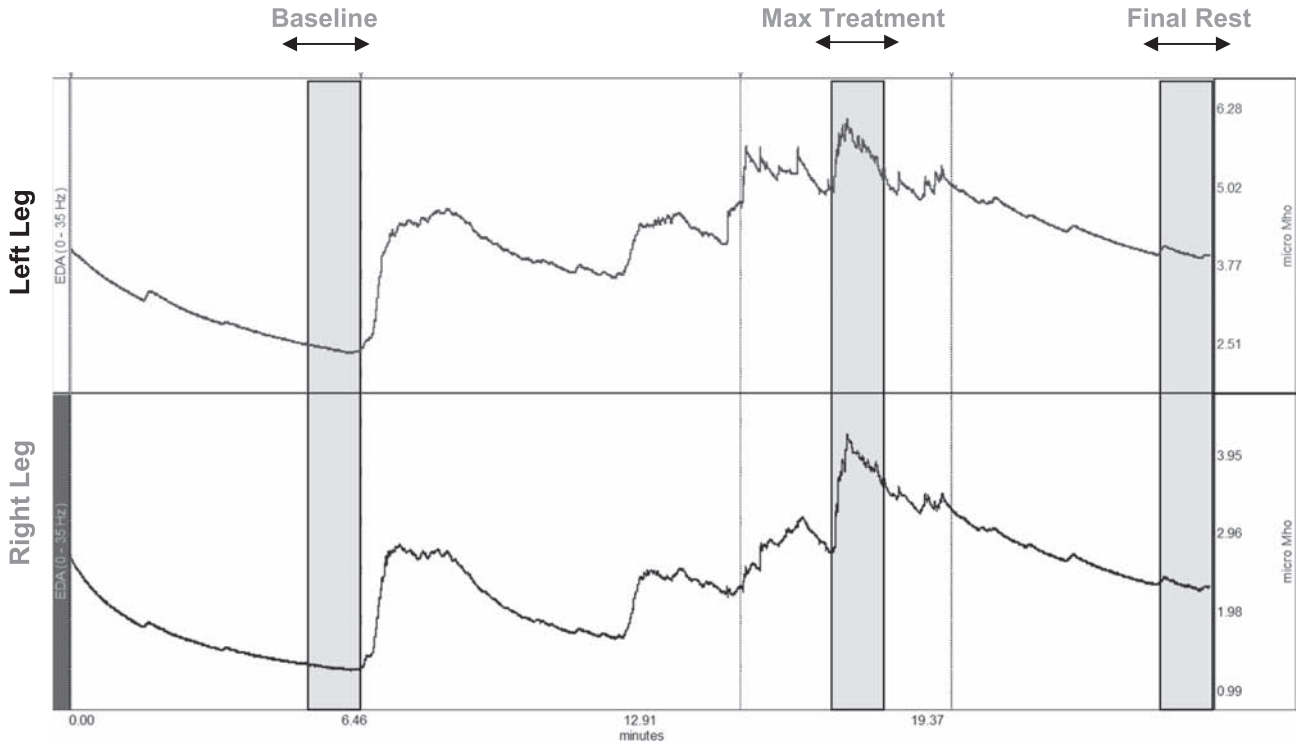

Fig 3. *Schemata of Biopac data recording from a participant, indicating the 1-minute data capture points within a single episode of care (baseline, during treatment, and final rest periods [in grey shading]).* EDA, *electrodermal activity/skin conductance.*

Table 2. *Illustrating the SCA Levels (in μmhos) and Percentage Change Response (SCR %) Within and Between Treatments and Associated PROMs (Functional Disability and Pain Intensity Scores)*

SCA Levels (in μmhos) (& SCR = % change from baseline)	Inception (n = 60)	Midpoint (n = 59)	Discharge (n = 59)
Baseline period			
Mean SCA level	82	98	100
SD	34.1	47.9	49.2
Range	15-156	13-224	15-199
CI 95%	73-91	85-110	87-113
Treatment period			
Mean SCA level (& SCR %)	230 (219%)	217 (160%)	172 (94%)
SD	85.0	83.2	66.4
Range	106-437	55-397	30-316
CI 95%	208-253	195-238	154-178
Final rest period			
Mean SCA level (& SCR %)	140 (86%)	162 (79%)	144 (55%)
SD	54.9	78.3	70.4
Range	34-259	41-389	28-297
CI 95%	125-154	142-182	125-162
Functional disability			
Mean ODI (%)	43%	16%	8%
SD	17.5	6.3	8.1
Range	16-86	4-34	0-30
CI 95%	38-47	14-17	6-10
Pain intensity			
NPRS (0-10)	7.5	2.7	0.3
SD	1.4	1.5	0.4
Range	4-10	0-6	0-1
CI 95%	7-8	2-3	0.2-0.4

CI, confidence interval; *NPRS*, numeric pain rating scale; *ODI*, Oswestry Disability Index; *PROM,* patient reported outcome measure*; SCA*, skin conductance activity; *SCR*, skin conductance response; *SD*, standard deviation.

functional disability was 43% (ODI) indicating moderate disability, with the average pain intensity level being 7.5 (NPRS 0-10). Throughout the program of care, ODI and pain intensity levels both reduced (by an average of 35% for ODI and by 7.2 out of 10 on NPRS). The mean number of treatments provided was 5.4 (±1.6).

Skin Conductance Measure Changes Within and Between Treatment Episodes

Descriptively, although baseline SCAs increased from inception through midpoint to discharge (82, 98, 100 μmhos), the contrary occurred during the "treatment" phases with sympathoexcitatory levels diminishing in intensity as the episodes of treatment progressed to discharge (230, 217, and 172 μmhos; SCRs 219%, 160%, and 94%, respectively). The final rest period SCAs were observed to remain relatively consistent throughout the program (140, 162, and 144 μmhos), although higher than baseline levels, this suggests some protraction of the immediate neurophysiological treatment response into the final rest period.

Inferential statistical analyses utilized a repeated measures analysis of variance of SCA levels with treatment phase (baseline, during treatment, and final rest periods) and episode of care (inception, midpoint, and discharge) being within participant factors. Results indicated differences between episodes of care and between treatment phases with differences between their interactions tested using Greenhouse-Geisser adjusted F-tests. Findings revealed a significant difference between phases of the individual treatment episodes ($F_{1.9,\ 109.8} = 322.23$, $P < .001$) and between different episodes of care ($F_{1.9,\ 109.9} = 4.66$, $P = .013$). Examination of interactions between treatment phases and episodes of care (utilizing the Greenhouse-Geisser epsilon factor correction) indicated that there were significant interaction effects ($F_{2.7,\ 157.2} = 19.31$, $P < .001$). Pair-wise comparisons between phases of treatment and episodes of care identified differences in SCA levels between all phases within each episode ($P < .0001$) with key interactions recognized during the treatment periods from the inception to discharge data capture points ($F = 4.24$, degrees of freedom [df] = 2, $P = .044$) and, in particular, between midpoint to discharge ($F = 8.66$, df = 2, $P = .005$) compared to inception to midpoint ($F = 1.29$, df = 2, $P = .261$) (Fig 4). Preliminary analyses of the nature of the treatment resulting in the maximum SCR indicated that 58% were as a result of a lumbar rotatory manipulation (HVLAT), 28% due to a mobilization with movement technique and 14% from a McKenzie extension exercise.[8]

Changes in Function (Oswestry Disability Index) and Pain Intensity (Numeric Pain Rating Scale) Between Treatment Episodes

From inception through midpoint to discharge, reported levels of pain intensity (Fig 5) and functional disability (Fig 6)

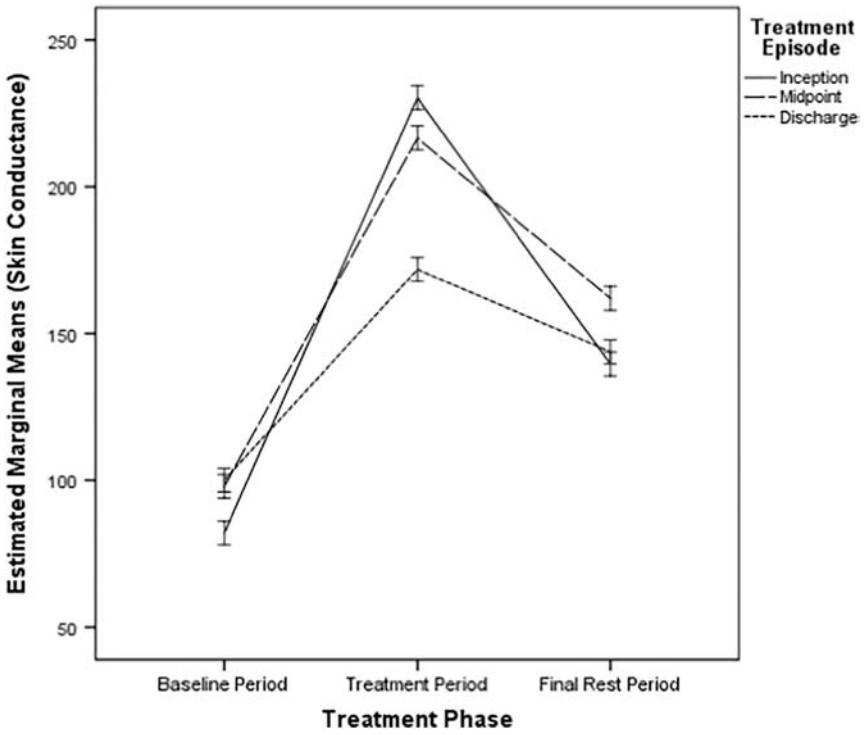

Fig 4. *Profile plot charting the skin conductance activity levels (means) within each treatment phase at the 3 different data capture points (treatment episodes) (with Error Bars: 95% confidence intervals).*

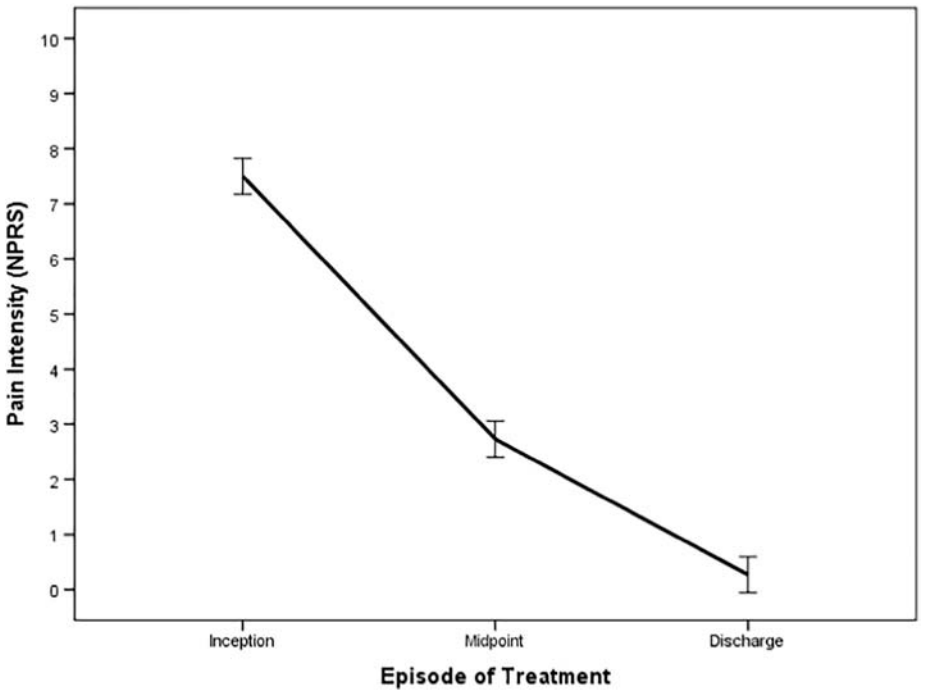

Fig 5. *Changes in pain intensity (NPRS) between treatment episodes.* NPRS, *numeric pain rating scale.*

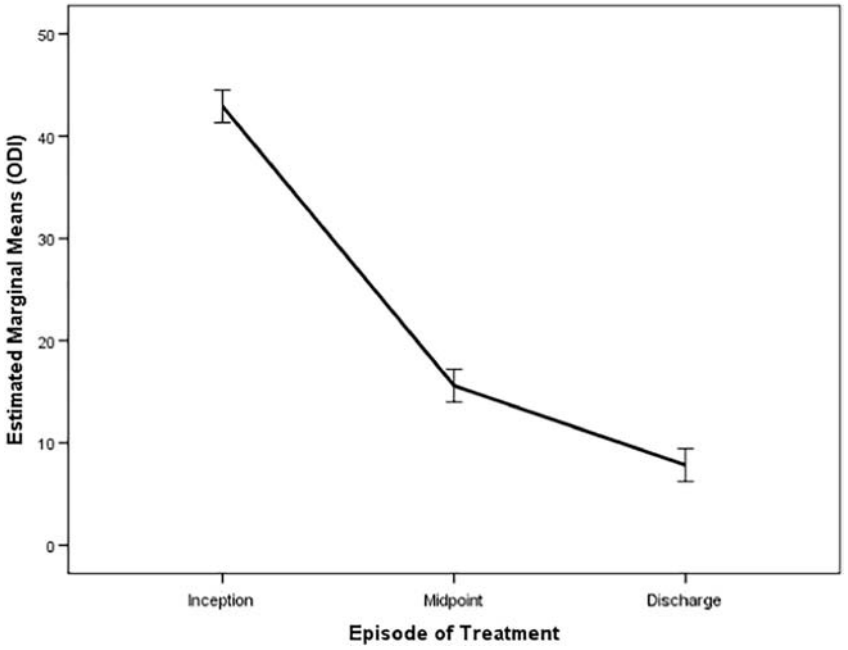

Fig 6. *Changes in functional disability (ODI) between treatment episodes.* ODI*, Oswestry Disability Index.*

were significantly diminished (NPRS: k = 119.02, df = 2, $P <$ .001 and ODI: F = 142.52, df = 2,175, $P < .001$, $R^2 = 0.62$). Furthermore, by discharge, 95% of patients reported a return to pre-LBP employment status, with the remaining 5% completing a 6-week program of phased return.

Correlations Between Skin Conductance Responses and Patient-Reported Outcome Measures (Pain and Function)

Skin conductance responses were compared to NPRS and ODI at each data capture point from inception to discharge. Statistically significant findings were identified only at inception, with a strong positive correlation between SCR and functional disability or ODI ($r = 0.82$, $P < .0005$) and a moderate positive correlation between SCR and NPRS ($r = 0.459$, $P < .0005$).

Discussion

This study is the first to report longitudinal changes in neurophysiological SNS activity levels within and between treatment episodes in an acute and subacute LBP patient population undergoing a course of guideline-endorsed multimodal physiotherapy. Key findings highlight 3 important observations in this patient cohort. First, within-session SC changes were significant during all "treatment" periods ($P = .044$) and revealed that the magnitude of sympathoexcitatory responses (SCRs) were greatest at inception (219% increase in activity levels from baseline). Pairwise comparisons of between-session interactions identified that responses significantly ($P = .005$) diminished in the magnitude of sympathoexcitation to midpoint (160%) and discharge (94%), with discharge measurements mirroring those seen in published normative studies[7] that recorded SC changes of 95% in their lumbar manipulation group. Second, the treatment identified as providing the maximum SCR (at each data capture point) was the manipulation technique (HVLAT), with an overall prevalence of 58% of all treatments performed, regardless of the point at which the manipulation technique was performed during the episode of care. Third, there were notable positive correlations between treatment SCRs and reported levels of functional disability ($r = 0.82$, $P < .0005$) and pain intensity ($r = 0.459$, $P < .0005$) at inception, indicating that patients with the highest magnitude of SC response were also those with higher levels of reported functional disability and pain intensities. Interestingly, whereas diminution in SCR through the course of treatment (inception, midpoint, and at discharge) appeared to correspond to reductions in functional disability (43%, 16%, and 8%, respectively) and reduced pain intensities (7.5, 2.7, and 0.8, respectively), these failed to meet significance levels, which may indicate that SCRs could represent a phenomenon not captured by PROMs, that PROMs are a blunt instrument and lack the sensitivity and specificity needed to detect the subtleties of change identified by SCRs, or, alternatively, that the study design and sample size were inadequate to reveal significant levels at these data capture points.

Previously reported normative[7] and patient[3] responses to the 2 types of MT treatments utilized in the present study (manipulation and repeated extension in lying exercise) revealed that the 2 cohorts (asymptomatic and symptomatic) were not analogous regarding the magnitude of responses to the 2 treatments. Notably, the patient cohort SCRs to a lumbar HVLAT technique were in excess of twice that of the normative group (216% and 95%, respectively). The 3-fold increase in magnitude of SCR with treatment of the patients presented in the current study supports these findings and the construct that patients (with acute and subacute LBP, with moderate to high levels of pain and disability) have an altered state of SNS arousal[17] when exposed to mechanical stimulation. It may be argued that this observation provides objective support for the central and spinal mechanisms of action of the manual therapy "model" advocated by Bialosky et al.[6] Furthermore, this clinical, symptomatic group demonstrated neurophysiological SNS responses that may be indicative of a sensitized DH that has been conceptualized by Woolf and Salter[11,12] as occuring as a result of stimulation and "up-regulation" of peripheral, nociceptive receptors, which was further evidenced by Boal and Gillette,[10] who confirmed the development of long-term neuroplastic potentiation changes in DH nociceptive neurons, specifically in patients with LBP. Bakkum et al[9] also found that experimentally induced hypomobile spinal segments in rats caused DH neuroplasticity, DH synaptic hyperactivity with resultant maladaptive central changes that occurred as a response to diminished mechanical stimulation within the joint receptors.

Considering these elements, within the context of the findings of the current study, it may be suggested that the LBP patients with hypomobile spinal segments (functional disability) and heightened nociceptive activation (pain) were initially observed to have augmented treatment SCRs when mechanically stimulated by MTs at inception, but, as symptoms abated toward midpoint and discharge, adaptations in nociceptor activity resulted in a reactive or neuroplastic "down-regulation" and diminished arousal state of the SNS[17] with resultant normalization of treatment SCRs by discharge, comparable to published normative cohorts (ie, 76% in Perry et al[7]). This might also explain the positive correlations, at inception, between SCRs and PROMs; however, the lack of significant findings at midpoint and discharge might suggest that these findings are simply a product of sampling violations (ie, no randomization). It may be hypothesized that SCRs may possess a unique measurement quality not captured by the PROMs in this study. Clearly, further systematic research exploring the nature and efficacy of responses to different elements of the outcome measures and the therapeutic interaction would help elucidate this construct. Furthermore, research into a chronic LBP cohort, with a potentially "centrally sensitized" neural state, might provide further insight into the neuroplastic adaptations that occur in long-term pain presentations.

It is worth noting that throughout this study the SCRs reported were in excess of the SRD value of 4.6% (SCA >0.315 μmhos) reported by Perry et al,[7] indicating that the within- and between-treatment responses observed were likely ascribable to the MT interventions undertaken rather than to measurement error and that treatment responses maintained into the final rest period were not a temporary, phasic phenomenon, thereby suggesting MT treatment effects may possess longevity in symptomatic populations. Furthermore, this study reported that effect sizes all exceeded the published minimum clinically important differences for the PROMs (NPRS >3.3 out of 10 and ODI >35.6 for complex intervention studies[18]), suggesting a meaningful change in patients' pain and function.

Limitations

The results of the present study should be considered in light of several limitations. Because of the design of this inquiry (a pragmatic, observational study) it was not possible to assign a true cause and effect relationship between treatment and response, thereby limiting any inferences that can be made from the statistical analyses. Although it is acknowledged that the inclusion of a control arm would have been informative regarding any neurophysiological changes resulting from no intervention (natural regression to the mean), analysis of SC control group data from previous published papers (n = 130 participants) revealed only a small variance in SC values (–1.01% to 3.20% change), indicating stability in "control condition" readings throughout the data collection periods of these studies. Furthermore, these "control group" levels of SC change values are below the SRD value (4.6%) mentioned earlier, which is a value beyond which any SC change can be considered independent of any measurement error or variability and, thereby, ascribable to the intervention under investigation.[7] Similarly, it may be argued that the absence of a "placebo treatment" compromises the assertion that observed changes were not solely due to the "laying on of hands" or increased arousal attributable to expectation of treatment. Thus, it is recommended that future studies be considered that explore the effects of placebo and treatment expectation, as this would further enhance professional knowledge in this area.

In addition, the use of a nonprobabilistic convenience sample of homogenous acute and subacute LBP patients could limit the external validity of the study to the broader (chronic) LBP population. No attempt was made to influence the order of the treatment interventions delivered to the patients. Although the types of treatment were specifically detailed (but not reported here) and were consistently performed between patients, the order of the prescribed treatments may have influenced the SCRs obtained. Counter-balancing[19] may have alleviated the effects of potential confounding, extraneous variables and may be

worthy of consideration for future complex intervention studies. Finally, it is acknowledged that the point of discharge varied from 3 to 8 because the reasons for discontinuing care were left to the discretion of the individual patient and therapist. Recommendations for future studies would be to identify and control clear, predetermined data capture points within a set time period and to perform the study on patients presenting with symptoms of greater than 12 weeks' duration, thereby facilitating greater generalization of the findings to all patient subgroups.

Conclusions

To the authors' knowledge, this is the first study to evaluate the effects of a guideline-endorsed, multimodal physiotherapy treatment on SCA levels, SCRs, and PROMs within an acute and subacute LBP patient population within a clinical environment. The results support anecdotal therapy results by demonstrating that patients exhibit neurophysiological treatment responses that reflect the existence of a symptom-related adapted or plastic state of DH sensitization that was particularly receptive to manipulative therapy intervention within a 4- to 8-week treatment program. Furthermore, the findings support the use of early therapeutic intervention to maximize the speed and magnitude of symptom abatement.

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Contributorship Information

Concept development (provided idea for the research): J.P.
Design (planned the methods to generate the results): J.P., A.G.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): A.G.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): J.P.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): J.P.
Literature search (performed the literature search): J.P.
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Practical Applications

- Initial therapeutic intervention responses correlated with heightened dorsal horn excitability, enhanced pain abatement, and timely functional restoration.
- Longitudinal diminution of neurophysiological responses to treatment correspond with symptom abatement, and responses seen in asymptomatic populations suggested neuroplastic adaptation to therapeutic stimulus.

References

1. National Institute for Health and Clinical Excellence (NICE). Low back pain: early management of persistent non-specific low back pain. Available at: https://www.nice.org.uk/guidance/cg88. Accessed December 12, 2016.
2. Parr S, May S. Do musculoskeletal physiotherapists believe the NICE guidelines for the management of non-specific LBP are practical and relevant to their practice? A cross sectional survey. *Physiotherapy.* 2014;100(3):235-241.
3. Perry J, Green A, Singh S, Watson P. A randomised, independent groups study investigating the sympathetic nervous system responses to two manual therapy treatments in patients with LBP. *Man Ther.* 2015;20(6):861-867.
4. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad Emerg Med.* 2003;10(4):390-392.
5. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine.* 2000;25(22):2940-2952.
6. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther.* 2009;14(5):531-538.
7. Perry J, Green A, Singh S, Watson PJ. A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. *Man Ther.* 2011;16(2):190-195.
8. Mckenzie RA, May S. *The Lumbar Spine: Mechanical Diagnosis and Therapy*, Vol. 2. Waikanae, New Zealand: Spinal Publications New Zealand Limited; 2003.
9. Bakkum BW, Henderson CNR, Hong SP, Cramer GD. Preliminary morphological evidence that vertebral hypomobility induces synaptic plasticity in the spinal cord. *J Manipulative Physiol Ther.* 2007;30:336-342.
10. Boal RW, Gillette RG. Central neuronal plasticity, low back pain and spinal manipulative therapy. *J Manipulative Physiol Ther.* 2004;27(5):314-326.
11. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science.* 2000;288:1765-1769.

12. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain.* 2011;152:S2-15.
13. Thomas J. *Australian Prescription Products Guide*. 31st ed. Hawthorn, Australia: Australian Pharmaceutical Publishing; 2002.
14. Koltyn KF. Analgesia following exercise: a review. *Sports Med.* 2000;29(2):85-98.
15. Perry J, Green A. An investigation into the effects of a unilaterally applied lumbar mobilisation technique on peripheral SNS activity in lower limbs. *Man Ther.* 2008;13(6):492-499.
16. de Campos TF. Low back pain and sciatica in over 16s: assessment and management NICE Guideline [NG59]. *J Physiother.* 2017;63(2):120.
17. Storm H, Fremming A, Ødegaard S, Martinsen ØG, Mørkrid L. The development of a software program for analysing spontaneous and externally elicited skin conductance changes in infants and adults. *Clin Neurophysiol.* 2000;111: 1889-1898.
18. Goertz CM, Pohlman KA, Vining RD, Brantingham JW, Long CR. Patient-centred outcomes of high-velocity, low-amplitude spinal manipulation for low back pain: A systematic review. *J Electromyogr Kinesiol.* 2012;22(5): 670-691.
19. Newell R, Burnard P. *Research for Evidence-based Practice in Healthcare*. 2nd ed. Oxford, UK: Wiley-Blackwell Publishers; 2011.