Author's response to reviews

Title: Neurophysiologic effects of spinal manipulation in patients with chronic low back pain

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Version: 3 Date: 5 July 2011

Author's response to reviews: see over
July 4th, 2011

Dear Dr. Lawrence,

Thank you for your time and efforts in handling our manuscript titled “Neurophysiologic effects of spinal manipulation in patients with chronic low back pain”. We have read and responded to all of the reviewer’s comments and we are hopeful that our revised submission will be acceptable for publication in BMC Musculoskeletal Disorders. Additionally, we have taken care to ensure the resubmitted manuscript is formatted as to the journals requirements. If you have any questions please do not hesitate to contact me.

Sincerely,

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Dear Reviewer 1,

Thank you for your time in reviewing and providing feedback on our manuscript. We have extensively considered and revised the manuscript based on your comments, and we feel that the overall quality and clarity of the manuscript has been improved. Accordingly, we are hopeful that this revised version will be met with a positive review from yourself and is suitable for acceptance in BMC Musculoskeletal Disorders. Below we provide a point-by-point response to each issue raised.

MAJOR COMPULSORY REVISIONS

Reviewer Comment:

Background

1. P3 lines 14-18: Many scientists and clinicians have long-postulated that manual therapies exert their biologic effects on segmental components of the central nervous system [13-22]. For example, more than 25 years ago it was noticed that deep somatic or visceral pain leads to local increases in muscle tone/spasm [23], and many authors have speculated that an increased stretch reflex gain underlies the increased muscle tone in painful muscles as is commonly observed in LBP [16-18, 24].

I’m not clear on the ideas here. In the first sentence, what does the concept of “segmental” refer to, eg, what is the nature of the segment (neural, vertebral, something else)? In the second sentence, the concepts of “deep pain” and “local increases” are presented. What does “local” mean? Does it refer to the superficial muscles overlying the location of the deep pain regardless of whether that pain is arising from deeper muscles or from an underlying viscera? These meanings should be clarified. That pain increases the stretch reflex gain in lumbar muscles in low back pain is not actually supported by the human literature as shown in reference 28 of this manuscript. In the low back, this has been supported by an animal study (Kang YM, Wheeler JD, Pickar JG. Stimulation of chemosensitive afferents from multifidus muscle does not sensitize multifidus muscle spindles to vertebral loads in the lumbar spine of the cat. Spine 2001 15;26 (14):1528-36)

Author Response: The phrasing “segmental” refers to segments of the nervous system (e.g., supraspinal vs. spinal), as denoted by the sentence stating “segmental components of the central nervous system.” This terminology is widely used in the field of applied human neuromuscular physiology (for example, the corresponding author has published numerous articles using this terminology previously, which is consistent with terminology used by many others—including John Rothwell, Janet Taylor, Simon
Gandevia, Roger Enoka, Guang Yue, Alvaro Pasual-Leone and others). In recognizing that the term segmental could easily be confused in this manuscript as referring to vertebral segments we have added a parenthetical example at the end of this statement to better clarify the meaning. With regards to the term “local” we have rephrased this sentence for clarity. It now reads as follows: “...deep somatic or visceral pain leads to increases in muscle tone/spasm in the surrounding musculature [23]...” Lastly, we have added a sentence to this section highlighting the work by Zedka as well as that by Kang as the reviewer mentions. This sentence reads as follows: “Interestingly, the limited animal {Kang, 2001 #256} or human {Zedka, 1999 #40} data that exists does not support this common clinical assertion.”

**Reviewer Comment:**

**Methods**

2. P5 lines 4-5: During the SM procedure special care was taken to document the study participants who exhibited an audible response.

Describe the special care that was taken for the documentation. More importantly, what method was actually used to determine the presence of a cavitation? How sensitive was it?

**Author Response:** We should state upfront that the *a priori* purpose of this study was not to specifically examine the physiological effects of SM with special emphasis on whether or not a audible response occurred *per se*. As such, our method for determining whether or not an audible response occurred was to simply take special care to listen and document if this did or did not happen (as opposed to using sophisticated biomedical engineering applications to determine this). We now note this is the revised article.

**Reviewer Comment:**

3. P 7 lines 20-22: The corresponding EMG responses were recorded, and the peak-to-peak amplitude of the reflex responses was averaged to assess stretch reflex excitability.

What exactly is meant by excitability? Are the authors referring to recruitment of additional motor units, or to an increase in the firing rate of the same motor units, perhaps both? This is an important consideration because measuring peak EMG amplitude is arguably not the most sensitive outcome measure to assess excitability of the motoneuronal pool for the following reason. The EMG response is a compound action potential representing the sum of voltages over time from the individual motor units. Peak amplitude will be a sensitive indicator if motor units are activated sufficiently synchronous in time (based upon considerations of simultaneous alpha-motoneuron activation and similar conduction velocities) such that the positive-going portion of one
unit’s action potential is not negated by the negative-going portion of a second unit’s. If not sufficiently synchronous, then even if more motor units are recruited, summation could reduce the peak amplitude. The authors are strongly encouraged to rectify and integrate their signal and compare the area under the EMG curve. This would represent the sum total of the muscle’s electrical activity. It would encompass both aspects of excitability: prolongation of the response due to an increase in discharge frequency of any given alpha motoneuron as well as recruitment of additional motor units.

**Author Response:** The term excitability is being used in a broad sense describing the overall magnitude of the evoked electrical response to standardized mechanical tapping. As illustrated in figure 2 and in our previous work (Goss et al., J Neuroscience Methods, 2011) our short-latency stretch reflexes evoked from the paraspinal muscles resembled compound muscle fiber action potentials with waveforms similar to those observed with electrically evoked M-max and H-reflexes. Accordingly, our responses did not resemble stretch reflexes similar to those we have observed in other muscles (e.g., soleus) in response to stretching the muscle by rapidly moving a joint (e.g., the ankle) through the range of motion. It is for this reason (the waveform characteristic) that we choose to quantify the stretch reflex as a p-p value (as is commonly done for Mmax and H-reflexes). We should note that others have also quantified the stretch reflex in this manner (e.g., Hjortskov et al., J Appl Physiol, 2005; Avela et al., J Appl Physiol, 1999, etc. [a PubMed search of “stretch reflex peak-to-peak amplitude” actually yields 43 hits).
the manipulation was given nearer the sacroiliac joint and at a substantial distance from the vertebral and spinal cord levels at which EMG activity was recorded, these issues should be considered in the interpretation of the data and presented in the Discussion.

**Author Response:** The reviewer has raised a good point regarding specifics of the manipulative procedure. We have revised our description based on these suggestions. Indeed we do maintain that the manipulation was delivered in a localized manner. The vertebral segments chosen for manipulation were chosen based on palpatory structural diagnosis assessing for position and motion restriction consistent with standard osteopathic structural diagnostic procedures. The manipulation force applied was localized to the dysfunctional vertebral segment utilizing alignments of force vectors secondary to subject positioning. We have added details of this nature to the methods in the revised version of the manuscript.

**Reviewer Comment:**

5. P9 lines 2-3: Eta-squared (#2) estimates of effect size are also reported to assist in data interpretation.

The authors provide no information in the Methods, Results nor Discussion how eta-squared was used to aid data interpretation.

**Author Response:** We have rephrased this statement to read as follows: “Eta-squared (\(\eta^2\)) estimates of effect size are also reported to provide the reader insight on the magnitude of effect of SM.”

5. P9 line 8: Data are presented as means ± SE, unless otherwise stated.

Presenting confidence intervals would be more informative and easier to interpret than the standard error. The authors should consider presenting the data as confidence intervals when they are using inferential statistics and standard deviation when their intent is to describe their experimental sample population.

**Author Response:** We have not made this change, as it was not a universal suggestion in that the other reviewer did not suggest this. If the Editor (or a reviewer) feels strongly that this change needs to occur we will be happy to comply.

**Reviewer Comment:**

Results
7. P9 line 7: Using a 0-10 visual analog scale, the chronic LBP patients rated their usual LBP as 4.0±1.2, their current LBP as 2.6±1.6, and their lifestyle change imposed from their LBP as 3.9±3.1. Additionally, they reported having LBP for a mean duration of 3.2±3.1 years, scored 5.9±4.3 on the Roland Morris Disability Questionnaire,[40] and scored 33.5±6.5 on the Tampa Scale for Kinesiophobia [41].

The methods section doesn’t describe the use of these tools. It should. How did the asymptomatic participants compare on these parameters?

**Author Response:** We have added a section in the methods describing the tools used to characterize LBP. We have also noted that the asymptomatic participants reported a zero out of 10 for their current level of LBP. We did not have these subjects complete all questionnaires though, making direct comparisons difficult.

**Reviewer Comment:**

8. P9 lines 13-14: SM did not alter the erector spinae MEP amplitude in patients with LBP (0.80±0.32 to 0.80±0.30 µV) or in asymptomatic controls (0.56±0.09 to 0.57±0.06 µV). (Figure 4; time main effect: p=0.61, #2=0.02; time x group interaction: p=0.62, #2=0.01).

MEPs appear higher in the LBP pain group compared to the asymptomatic controls. Is this meaningful? A 2-way ANOVA is reported but only the main effect of time is reported. The group effect should be reported as well. This would address whether the MEPs are significantly different between the groups although the interpretation is not straightforward because there is an interaction effect.

**Author Response:** We now report the group main effects for both the MEP and stretch reflex outcomes. There was no significant group main effects observed. As the reviewer notes, there was a reasonable mean difference for the MEP amplitude between groups at baseline (.80 vs .56 30 µV); however, this difference was largely driven by one outlier with a higher absolute value in the LBP group.

**Reviewer Comment:**

9. P9 section starting on line 21: In this section, differences in MEP and the stretch reflex between those with and without an audible sound are presented regardless of group assignment.

Differences in MEP and the stretch reflex between those with and without an audible within each experimental group (the healthy and the LBP group) would be important and potentially interesting to know. It could indicate whether the nervous system of LBP is altered in a way that it makes the effect greater or lesser compared to asymptomatics.
**Author Response:** We have added two sentences regarding the magnitude of change for both the MEPs and stretch reflexes for each patient group that also exhibited an audible response. In our opinion there is nothing noteworthy per se along these lines.

**Reviewer Comment:**

Discussion

10. P12 lines 1-4: It is also important to note that the reduction in the magnitude of the short latency reflex response was independent of any pathology (i.e., both healthy and LBP groups had similar responses). This suggests that the down regulation of the reflex is due to the mechanical forces applied to the periarticular tissues more than to some ability to restore motion to a joint segment.

This is premature to state this. No pathology was actually shown. No data are provided showing that either the healthy or LBP group had or did not have a motion problem that was in turn affected by the manipulation. The only inclusion criterion in this study was LBP. No evaluation was made of motion.

**Author Response:** This statement has been removed.

MINOR ESSENTIAL REVISIONS

**Reviewer Comment:**

Background

11. P3 lines 14-16: Many scientists and clinicians have long-postulated that manual therapies exert their biologic effects on segmental components of the central nervous system [13-22]. For example, more than 25 years ago it was noticed that deep somatic or visceral pain leads to local increases in muscle tone/spasm [23],

It is not clear to this reviewer what the segmental in “segmental component” of the central nervous system refers to, even with the example given in the second sentence. Does it refer to a type of neuron in the CNS, a spinal cord level relative to a dermatomal level where the manual therapy is given? Please clarify.

**Author Response:** Please see response to point 1.

**Reviewer Comment:**

12. P3 lines 18-22: However, the reflex activity of human back muscles has received little attention [25-28], and to our knowledge, no studies have quantified the effects of spinal
manipulation (SM; the most common manual therapy used treat LBP [29,21 30]) on the stretch reflex excitability of the low back muscles despite this being such a commonly touted mechanism of action.

It would be appropriate to include reference to a very early work: Dimitrijevic MR, Gregoric MR, Sherwood AM, Spencer WA. Reflex responses of paraspinal muscles to tapping. J Neurol Neurosurg Psychiat 43: 1112-1118, 1980.

**Author Response:** This reference has been added.

**Reviewer Comment:**

13. P3 lines 23-25: The scientific understanding of the neurophysiologic characteristics of the human low back muscles has historically been hindered by the lack of experimental techniques to examine these muscles function in vivo.

Edit needed: “these muscles function”. Grammatically, is “muscles” supposed to be a possessive form?

**Author Response:** This has been corrected.

**Reviewer Comment:**

Methods

14. General. The time interval between the manipulation and each assessment should be provided.

**Author Response:** This has been added.

**Reviewer Comment:**

15. P5 lines 1-2: quantify MEP amplitude (as an index of corticospinal excitability), and electromechanical tapping to quantify short-latency stretch reflex amplitude (as an index of Ia reflex pathway excitability).

What was tapped?

**Author Response:** The lumbar paraspinal muscles were tapped and this has been clarified.
16. P5 line 12: LBP for at least 12-weeks, and to have previously sought physician care, chiropractic care or physical

Change “physician” care to “medical” care.

**Author Response:** Done.

**Reviewer Comment:**

17. P13 line 13: therapy for treatment of their LBP. Individuals were excluded if they had a history of spinal surgeries, “surgeries” should be singular because 1 surgery would presumably suffice for exclusion.

**Author Response:** This has been corrected.

**Reviewer Comment:**

18. P5 line 18: loss or an elevated temperature, had received any manual therapies intervention in the past 1-month, “therapies” should be singular.

**Author Response:** This has been corrected.

**Reviewer Comment:**

19. P5 line 25 and onto next page: In brief, bipolar surface electrodes were located longitudinally over the muscle at the vertebral level of L2 and L4 on shaved and cleaned skin with a longitudinally over the muscle at the vertebral level of L2 and L4 on shaved and cleaned skin with a reference electrode located on the anterior superior iliac spine (Ag–AgCl, potential sensitive area of 22- mm, 6-cm center-to-center interelectrode distance; 2015 Nikomed Trace1, Hudson Valley, PA).

When it is stated that the electrodes were “located”, does it mean “placed”? Located implies that the electrodes were found on the muscle. Does “longitudinal” mean they were placed parallel to the spine’s long axis? Provide additional description as to where the electrodes were placed. For example, when does L2 and L4 refer to the spinous process? How far lateral to the L2 and L4 landmark were the electrodes placed? If the interelectrode distance is fixed at 6cm, then perhaps only one electrode placed at a reference landmark and the second landmark wound up 6 cm away. Please clarify. Was the patient grounded? Did the electrodes record differentially?

**Author Response:** We have provided further detail in the section, and it now reads as follows: “Electrical signals were recorded bilaterally from the erector spinae (ES)
muscles as we have previously described [33]. In brief, bipolar differential surface electrodes (Ag–AgCl, potential sensitive area of 22-mm; 2015 Nikomed Trace1, Hudson Valley, PA) were placed parallel to the spine’s long axis with one electrode positioned at L2 and the other positioned 6-cm directly below (6-cm center-to-center interelectrode distance). These electrodes were placed ~ 2-3 cm lateral of the spine over the belly of the erector spinae muscles. A reference electrode was placed over the anterior superior iliac spine. The electromyogram (EMG) signals were amplified (1000x), band pass filtered (10–500 Hz), and sampled at 5,000 Hz using a 16-bit data acquisition system (MP150, BioPac Systems Inc.). Electrodes were left in place throughout the duration of the testing session.”

**Reviewer Comment:**

20. P6 lines 12-13: The center of a custom-modified 110-mm double cone coil with a laser attachment system (The Magstim Co. Ltd., Whitland, England) was positioned over the vertex.

State the intent behind the placement of the double cone coil.

**Author Response:** This statement has been completed.

**Reviewer Comment:**

21. P6 lines 24-25 and onto the next page: During all analyses we visually analyzed the EMG traces to ensure that the TMS reflex responses did not occur in temporal relation with the electrocardiogram signals (to avoid interference with the EMG signals), and in the rare instance that this did occur the MEP was excluded from analysis.

The motor evoked potential evoked by transcranial magnetic stimulation is not a “reflex” response in the traditional sense of the word reflex which includes an afferent arm, central integration and a motor response. Does this mean that on occasion the MEP average for a given individual was obtained from less then 10 pulses? The number excluded should be provided in some form, perhaps the maximum number excluded and in how many participants.

**Author Response:** We removed the word “reflex”. We have also provided more details about having to exclude trials based on the EKG interference. This occurred in rare occasions, and in no more than one trial per a given subject.

**Reviewer Comment:**

22. P7 lines 2-4: Following the baseline TMS testing protocol the stretch reflex testing
protocol was performed and study participants then received SM. Ten minutes after receiving SM the TMS protocol was then repeated. I assume that in addition to repeating the TMS protocol, the stretch reflex testing protocol was repeated as well. This should be stated “Ten minutes after receiving SM” is a dangling modifier. The “TMS protocol” did not receive the TMS, the participant did.

**Author Response:** This statement has been rephrased.

**Reviewer Comment:**

23. P7 lines 5-6: Stretch Reflex. When a muscle is rapidly stretched, a short-latency stretch reflex is elicited due to the excitation of Ia afferent fibers within the muscle spindles [38].

Ia afferent fibers are not actually located within the muscle spindle. Wording should be edited to accurately describe the relationship. The muscle spindle is innervated by the afferent fibers. The receptive endings of the afferent fibers terminate in the spindle.

**Author Response:** This has been restated for clarity and accuracy.

**Reviewer Comment:**

24. P7 lines 22-23: A mark was made with indelible ink on the skin at the site of the tapping to ensure pre and post measurements were elicited at the same location.

Weren’t the measurements made at the EMG electrodes which were fixed in place? Do you mean that you ensured that the pre and post measurements were elicited from tapping at the same location? More simply, you ensured that tapping was applied to the same site by placing mark at the site.

**Author Response:** This has been restated for clarity and accuracy.

**Reviewer Comment:**

25. P7 lines 23-25 and P8 lines 1-3: During all analyses, special care was taken to ensure that the stretch reflex responses did not occur in temporal relation with the electrocardiogram signals (to avoid interference with the EMG signals), and in the rare instance that this did occur the trial was excluded from analysis. Following the baseline TMS and stretch reflex testing protocols study participants received SM, and ten minutes after the SM the TMS protocol was repeated followed by the stretch reflex testing protocol.
How did you or could you ensure that the stretch reflex response did not occur in relation to the EKG signal. Did you adjust the timing of the tapping so it did not coincide with the pulse? Much of the information contained here is redundant with what has been expressed at the end of the Transcranial Magnetic Stimulation section. The appropriate portions should be combined to remove the redundancy.

**Author Response:** We removed the last two sentences to avoid redundancy. We ensured that the stretch reflex response and the EKG signal did not temporally overlap by visually inspecting the EMG signal. As illustrated in Figure 2, the stretch reflexes evoked with our approach appeared like a compound muscle fiber action potential, and as such it was easy to determine if this overlapped or occurred in close temporal proximity with an EKG signal.

**Reviewer Comment:**
26. P8 lines 15-18: Statistical Analysis. Mixed-model analysis of variance techniques were utilized to determine the effect of the independent variables (i.e., within-subjects factor: time; between subjects factor: patient group; audible response group) on the dependent variables (MEP amplitude and short-latency stretch reflex amplitude).

The levels of each independent variable should be provided. Presumably there are 2 levels of time (before and after manipulation), 2 levels of patient group (healthy vs LBP) and 2 levels of audible response (yes vs. no).

**Author Response:** This information has been added.

**Reviewer Comment:**
27. P8 line 17: subjects factor: patient group; audible response group) Factor should be plural in that two factors were analyzed.

**Author Response:** This has been changed.

**Reviewer Comment:**
28. P8 line 22: significant main effects and/or interaction terms

When there are significant interaction effects, interpretation of significant main effects is not straightforward because the main effect consequently depends upon level of the 2nd factor. Consider changing the “and/or” should be changed to an “or”.

**Author Response:** This has been changed.
Reviewer Comment:  
Results  
29. P9 line 24: whereas nine did not (4 participants with LBP, and 4 controls).  
Math error: 4+ 4 do not add to nine as stated.  
**Author Response:** This has been corrected (it should have read 5 participants with LBP and 4 controls).

Reviewer Comment:  
30. Figure 6. Does the presumed effect of gamma activation affect only the indirect excitatory input to E and not the direct input to alpha? The legend implies there is only input from S to E but the figure shows input from S to E and to alpha. Make the figure consistent with the legend.  
**Author Response:** We have revised the figure legend to state that both direct and indirect excitatory inputs project from the spindles to the alpha-motorneurons.

Reviewer Comment:  
Discussion  
31. P10 line 24 and P11 lines 1-3: Many authors have hypothesized that SM functions via the pain-spasm-pain model by reducing the underlying nociceptive stimulus and consequently attenuating the stretch reflex, with the end organ effect being an overall reduction in muscle activity [43-48].  
These studies should be presented here. (also see comment regarding P3 Lines 14-18)  
**Author Response:** In the revised version of the manuscript we now discuss and reference these studies in this paragraph.
Reviewer Comment:

32. P11 lines 9-10: Although our observation of no pre- versus post-difference in patients with chronic LBP or asymptomatic controls I think this is inaccurately stated. The sentence indicates there is no pre-difference versus post-difference (based upon the placement of the hyphens follow pre- and post-). I believe the difference being described is pre- versus post-manipulation.

Author Response: This has been corrected.

Reviewer Comment:

33. P11 lines 17-20: It has been hypothesized that the rapid stretch of the periarticular muscles and connective tissue associated with SM causes the reduction in spinal reflexes; however, to our knowledge no previous studies have reported differential physiologic effects dependent upon whether SM results in an audible response.

Provide a reference for this hypothesis. There is at least one such study: Teodorczyk-Injeyan JA, Injeyan HS, McGregor M, Harris GM, Ruegg R. Enhancement of in vitro interleukin-2 production in normal subjects following a single spinal manipulative treatment. Chiropr Osteopat 16: 5, 2008

In addition, the authors should be familiar with and consider including the following paper apropos the topic of audible sounds and its relationship to joint movement. Cramer GD, Ross K, Pocius J, Cantu JA, Laptook E, Fergus M, Gregerson D, Selby S, Raju PK. Evaluating the relationship among cavitation, zygapophyseal joint gapping, and spinal manipulation: an exploratory case series. J Manipulative Physiol Ther 34: 2-14, 2011

Author Response: References for the statement are now provided, and we have also added several sentences related to the Cramer paper.

Reviewer Comment:

34. P11 lines 21-22: alters the short-latency stretch reflex- a critical segmental component of the pain-spasm-pain neuropathway illustrated in Figure 5

The neuropathway is shown in Figure 6 not Figure 5.

Author Response: This has been corrected.
Reviewer Comment:

35. P11 lines 23-24: As stated before, the short-latency stretch reflex occurs in response to a muscle being rapidly stretched, which excites the Ia afferent fibers within the muscle spindles [38].

It would be appropriate to give credit to those that discovered this pathway, which substantially predates the 2009 study referenced here.

Author Response: We now reference a Liddell and Sherrington paper from 1924.

Reviewer Comment:

36. P12 lines 1-3: It is also important to note that the reduction in the magnitude of the short latency reflex response was independent of any pathology (i.e., both healthy and LBP groups had similar responses).

Again, as commented on above with regard to P9, the section starting on line 21, it would add further insight to know if indeed the magnitude of the reduction was independent of any pathology by comparing the healthy and LBP groups. However, no pathology was actually identified in this study.

Author Response: This statement has been removed.

Reviewer Comment:

37. P12 lines 8-15: When a single pulse transcranial magnetic stimulation stimuli is applied to the motor cortex at an intensity above motor threshold, high-frequency indirect waves (I waves) are elicited in the corticospinal tract [53], which are modifiable by many mechanisms including neurotransmitters (i.e., glutamate, GABA), modulators of neurotransmission (i.e., acetylcholine, norepinephrine, and dopamine) [36], and interneurones contacted by corticospinal tract cells [54] with the actual efficacy of the corticomotoneuronal synapse itself demonstrating some activity-dependent changes [55] all functioning to influence the amplitude of the MEP.

This is a rather unwieldy sentence in terms of ideas presented. The sentence should be unpackaged. When this is done it may become evident that some of the ideas are not relevant or important to the overall point of the paragraph.

Author Response: We completely agree with the reviewer. We have rephrased this sentence to read as follows: “When a single pulse transcranial magnetic stimulation stimuli is applied to the motor cortex at an intensity above motor threshold, high-frequency indirect waves (I waves) are elicited in the corticospinal tract [55], which are modifiable by many mechanisms (i.e., glutamate, GABA, acetylcholine, etc.) [38] that
influence the amplitude of the MEP."

**Reviewer Comment:**

38. P12 lines 23-25: Additionally, in our work as well as that conducted by Dishman et al. it is possible that segmental changes in the nervous systems excitability (e.g., cortical level changes) as the MEP amplitude elicited 1 using single-pulse transcranial magnetic stimulation can be influenced at both the cortical and spinal levels.

To this reviewer “segmental changes” refers to the vertebral column and spinal cord yet cortical level changes are introduced as an example of a segmental change. Then at the end of the sentence segmental level refers to spinal level. The term “segmental” appears to have no specific meaning and one wonders why it is even used at all. Please clarify

**Author Response:** Please see response to comment 1. If the reviewer feels strongly regarding the terminology we will be more than happy to rephrase these statements.

**Reviewer Comment:**

39. References All references should be checked carefully for proper format, spelling and grammar. For example:

Ref 29: Typo: vertebreal

Ref 30: Misspelling: chiopractic

Ref 30: Extra punctuation: United Stated. . Greeley (2 periods)

**Author Response:** These corrections have been made.

DISCRETIONARY REVISIONS

**Reviewer Comment:**

General

40. It is surprising that the M2 component of the stretch reflex (the long latency component that occurs via a transcortical loop (as provided in reference 38)) was not studied or mentioned. Because TMS is testing for cortical changes, the M2 would have complemented the stretch reflex portion of the study.

**Author Response:** We have not observed consistent and reliable M2 responses in our previous work in the lumbar muscles, and thus did not attempt to examine this in this
Background

41. P3 lines 9-11: Over the past decade there has been growing scientific evidence supporting the clinical effectiveness of manual therapies in treating LBP [6-12]. While clinical evidence supporting the efficacy of manual therapies has emerged, little scientific evidence has been offered to explain the effects and mechanisms underlying these treatments.

From a clinical research perspective, the terminology used here should be reconsidered. “Effectiveness” studies and “efficacy” studies often address different issues. In the above sentences, references that support the “efficacy” of manual therapies should be provided. These would likely be distinct from the evidence for the “effectiveness” of manual therapies provided in the previous sentence.

**Author Response:** The reviewer has made a good point, and we have revised this statement to reference both efficacy and effectiveness studies, respectively. In reviewing these papers there is sometimes a fine line in classifying a specific paper/report into one of these categories, but we in essence classified multi-site investigative teams as effectiveness studies, and studies performed at a single-site in a more controlled setting as efficacy studies.

**Reviewer Comment:**

42. P4 lines 10-15: The role of the audible response in determining treatment effects has long been a matter of intense debate. Some studies have previously reported that an audible response is not necessary to improve clinical outcomes [33, 34], however, some have reported increased joint laxity and joint motion following manipulation that results in an audible sound [35] but few studies have investigated if the physiologic response is dependent on the manipulation causing an audible joint sound.


**Author Response:** Reference to this paper has been added to the revised version.

**Reviewer Comment:**
Methods

43. P6 lines 7-8: TMS pulses were delivered at the vertex of the skull similar to our previous description (Figure 1) [31]. I suggest adding a phrase indicating the purpose of the TMS pulses, namely pulses were delivered to evoke EMG activity in the lumbar erector spinae. This would make the intent clear and parallel the presentation of the purpose of the mechanical tapping in the next section of the Methods.

**Author Response:** This has been rephrased.

Discussion

44. P14 lines 4-6: This finding provides insight into the mechanism(s) of action of spinal manipulation, and suggests that spinal manipulation may mechanistically act by down regulating the gain of the muscle spindles and/or the various segmental sites of the Ia reflex pathway.

Does this imply that if spinal manipulation were delivered to an individual without a motor control problem and in a fashion that led to an audible release, it could have detrimental consequences for a “normal person” by down regulating this important feedback pathway?

A topic that might be considered is whether the audible release, because it affected the stretch reflex amplitude in both groups, suggests that the therapeutic effects of the manipulation have nothing the changes in spindle input because it occurred in a group without an apparent problem? This is where it might be important to know if the magnitude of the changes in stretch reflex amplitude were different between those with and without low back pain in the presence of a cavitation.

**Author Response:** At the end of the methods section we now state that the magnitude of change in the stretch reflex between the two groups of subjects who exhibited an audible response were similar. We do not feel the referenced statement implies that SM in 'normal persons' has detrimental consequences. A statement of this nature would be highly controversial and speculative, particularly when one considers that there are no well established normal (or abnormal) clinical values for a measurement of this nature.
Dear Reviewer 2,

Thank you for your time in reviewing and providing feedback on our manuscript. We have extensively considered and revised the manuscript based on your comments, and we feel that the overall quality and clarity of the manuscript has been improved. Accordingly, we are hopeful that this revised version will be met with a positive review from yourself and is suitable for acceptance in BMC Musculoskeletal Disorders. Below we provide a point-by-point response to each issues raised.

**Reviewer Comment:**

Major Compulsory Revisions

1. The methods used to identify/recruit the asymptomatic subjects (Page 5, Lines 10-12) needs to be described.

**Author Response:** This information is now provided in the “Study Participants” section, which now states: “The asymptomatic controls were matched for age, sex, and body mass index to the LBP patients. The control subjects were recruited by word of mouth and electronic mailing to the broader university community. To be included in the study, the asymptomatic control subjects had to report no history of LBP and rate their current LBP a zero on a 0-10 visual analog scale.”

**Reviewer Comment:**

2. The section “Study Participants Descriptive Statistics” is incomplete. The age range, mean age, and BMI for both the LBP and asymptomatic subjects should be provided separately, rather than combining the groups and estimating the values (e.g., the current paper reports these results in the statement, “...and on average both groups were ~23-24 years old with a BMI of 23”). This could be done as a table if preferred. Alternately, a table showing the values for each subject with the values for the “matched” subject in the same row could be provided. At a minimum, further description of the values for each group and the similarity or lack of similarity should be described. If the values for the two groups are different, the reasons for the differences and how the differences may or may not have affected the results should be provided.
Author Response: This information has been added to the section titled “Study Participants’ Descriptive Statistics”. It should be noted that there were no differences in age, height, weight or BMI between the groups.

Reviewer Comment:

Minor Essential Revisions

1. The authors should discuss why chronic low back pain (LBP) was chosen, rather than acute LBP. The neurophysiologic responses may be different between these two groups so the reason for choosing chronic LBP should be discussed, even if the discussion is brief.

Author Response: The reviewer raises a very good point, and in the limitations paragraph of the discussion we refer to this issue by stating: “Additionally, we chose to study chronic LBP patients (as opposed to acute or sub-acute LBP patients) due to the staggering economic costs that are associated with chronic LBP and the fact that many patients with chronic LBP seek manipulation therapy as a treatment option for their LBP [5]. However, it is possible that the neurophysiologic responses may be different if other groups of LBP patients had been studied as patients with LBP symptom duration for < 16 days are reported to be more likely to respond favorably to SM {Childs, 2004 #261}.”

Reviewer Comment:

2. The method used to determine if an audible joint sound was present during the SMT needs to be described in the paper. That is, did the person performing the SMT record whether or not an audible sound was heard, and if so when was the finding was noted (e.g., immediately after the procedure). Also, was the patient asked if he/she heard a joint sound, and if so, was the patient blinded to the response of the clinician?

Author Response: We have added greater detail regarding this, which now reads as follows: “During the SM procedure the treating physician and at least one other researcher took special care to listen during the SM procedure, confer with each other, and document the study participants who exhibited an audible response. This documentation occurred immediately following the SM procedure, but the subject was not consulted regarding whether they heard an audible response nor were they aware that we were documenting these responses.”

Reviewer Comment:

3. The outcome measures reported in the section of the Results entitled, “Study
Participants Descriptive Statistics” (i.e., visual analog scale[s], lifestyle change imposed from LBP, Roland Morris Disability Questionnaire, and Tampa Scale for Kinesiophobia) should be described in the Methods along with when these instruments were administered, and how these outcomes were summarized for reporting in the Results.

**Author Response:** Further details on these surveys are provided in the methods section now titled “Characterization of Low Back Pain.”

**Reviewer Comment:**

4. Also, in the section “Study Participants Descriptive Statistics,” several clinical values (VAS, Roland Morris, etc.) are reported for the LBP group only. Apparently these outcomes were not assessed for the asymptomatic subjects. Either the values for the asymptomatic subjects should be provided or a brief reason why these values were not obtained should be provided (i.e., how were the “asymptomatic subjects” determined to be asymptomatic; one or several questions administered, etc.).

**Author Response:** We now note that the asymptomatic participants reported a zero out of 10 for their current level of LBP (this was an inclusion criteria). The reviewer is correct in that we did not have these asymptomatic control subjects complete all questionnaires though—making direct comparisons between the groups difficult. However, our rationale for obtaining these measures was simply to describe and characterize the patient population (as opposed to making group comparisons per se).

**Reviewer Comment:**

5. Page 9, Line 24 – change “4 participants with LBP” to “5 participants with LBP” (i.e., the LBP and asymptomatic subjects without an audible sound during SMT should total nine subjects, based on the statement immediately preceding these values).

**Author Response:** This has been corrected.

**Reviewer Comment:**

6. Page 12, Lines 8-15 – This is a very long run-on sentence, please revise.

**Author Response:** This sentence has been revised and shortened. It now reads as follows: “When a single pulse transcranial magnetic stimulation stimuli is applied to the motor cortex at an intensity above motor threshold, high-frequency indirect waves (I waves) are elicited in the corticospinal tract [55], which are modifiable by many mechanisms (i.e., glutamate, GABA, acetylcholine, etc.) [38] that influence the amplitude of the MEP.”
Reviewer Comment:

7. Page 12, Line 12 – change “interneurones” to “interneurons”

Author Response: This word has actually been deleted based on a suggestion from reviewer 1.

Reviewer Comment:

8. Figures 4 and 5 are of poor quality (i.e., blurry) at least on the pdf. The quality of these important figures should be checked and if necessary improved.

Author Response: The resolution of these files has been improved.

Reviewer Comment:

Discretionary Revisions

1. Add term “audible joint sound” or “audible release” to Key Words even though this is not a MeSH term. Because the key finding was related to audible joint sounds, adding this term to the Key Words should help those interested in audible joint sounds find the paper more easily.

Author Response: This has been added.

Reviewer Comment:

2. Page 3, Line 10 – change “little” to “less.” There is a growing body of basic science research related to mechanisms of action of spinal manipulative therapy (SMT), as evidenced by the work of authors such as Pickar, Triano, Khalsa, Henderson, Ross, Cramer, and others.

Author Response: This has been changed.

Reviewer Comment:

3. Page 3, Line 20 – add “to” between “used” and “treat”

Author Response: This has been changed.
Reviewer Comment:

4. Page 5, Study Participants: Further detail on the nature of the subject screening and history and physical examination procedures for determining inclusion/exclusion of participants would be helpful. That is, how was initial screening conducted, did the study use the standard history and physical examination procedures of the clinical facility or were these procedures unique to this study; if a specialized examination was performed, what was emphasized in the exam, were the history and physical examination conducted on the same day of primary data collection for the study or a separate day, and when was informed consent administered.

**Author Response:** We have added a section to the methods that describes this process, which reads as follows: “History and Physical Examination. Interested participants completed a standard medical history form during the inclusion and exclusion screening process. On the day of testing, a physical examination was also completed. Here, subjects were assessed in the standing, seated, and supine positions to evaluate for the presence of somatic dysfunction in the thoracic, lumbar, sacral, or pelvic regions. This involved a palpatory screening assessment for alterations in tissue texture change and alterations in normal regional motion, followed by more detailed palpatory diagnostic procedures designed to localize the specific dysfunctional spinal segment or segments in each of the subjects. These palpatory procedures utilized normal landmark identification in the named regions and motion testing at a vertebral segmental level to determine the extent and severity of motion restriction along with increases in tissue hypertonicity and/or tenderness to palpation.”

Reviewer Comment:

5. Page 6, Line 11 – “nasinon” should be “nasion”

**Author Response:** This has been changed.

Reviewer Comment:

6. Page 8, Line 8 – “participation” should be “participants”

**Author Response:** This has been changed.

Reviewer Comment:

7. Page 8, Line 21 – “-level” should be “level”
**Author Response:** This has been changed to read “alpha-level”.

**Reviewer Comment:**

8. Page 10, Line 10 – suggest “virtually no” be changed to “few.” For example, H-Reflex studies on LBP subjects have been performed by Dishman et al. (referenced in the paper) and Cramer et al. Other studies assessing various neurologic outcomes as primary or secondary outcome measures likely exist as well.

**Author Response:** This has been changed.

**Reviewer Comment:**

9. Page 11, End of Line 20 through Line 22: This is one of the most important statements in the Discussion, yet one of the most awkwardly written sentences in the (otherwise well-written) paper.

**Author Response:** We have rephrased this sentence to read as follows: “Thus, our finding that SM alters the short-latency stretch reflex—a critical component of the pain-spasm-pain model of LBP (Figure 6)—only when an audible response occurs is novel.”

**Reviewer Comment:**

10. Page 12, Lines 4-6 – the reason for the changes in reflex activity associated with subjects having the audible release during SMT could also be that the joint surfaces in the audible release joints may gap (separate) more suddenly during SMT. This increased rapidity of joint gapping may be related to the production of an audible release (may answer why some joints have an audible release and others do not). The increased rapidity of joint gapping could be due to break-up of small adhesions present even in normal joints or due to increased muscle or connective tissue tension surrounding those joints before SMT. Consequently, “restoring motion to a joint segment” or increased speed of motion in a joint segment could conceivably be related to the production of an audible release and the subsequent changes in reflex activity found by these investigators.

**Author Response:** We thank the reviewer for this excellent suggestion. In the revised version we have added mention of this by stating at the end of this paragraph: “. It is also possible that the change in reflex activity associated with subjects having an audible release during SM may relate to gapping in the joint surfaces, as it was recently shown that vertebral segments that cavitated during SM gapped (separated) more than those that did not {Cramer, 2011 #260}. This greater joint gapping could result in the break-
up of small adhesions present even in normal joints, or due to increased muscle or connective tissue tension surrounding those joints, before SM. Consequently, SM that results in an audible response may conceivably function to restore greater motion to a vertebral segment (as opposed to SM that does not result in an audible response), and this biomechanical effect could result in subsequent changes in reflex activity as we observed.”

**Reviewer Comment:**

11. Page 15, Lines 4 and 7 – change “secured” to “secure”

**Author Response:** This has been changed.

**Reviewer Comment:**

12. Legend of Figure 6, Line 6 – change “(s)” to “(S)” (upper case to match figure)

**Author Response:** This has been changed.

**Reviewer Comment:**

13. Page 9, Line 6 – change Participants to Participants’ in the subtitle of this line.

**Author Response:** This has been changed.