Reviewer’s report

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

Version: 1 Date: 3 May 2011

Reviewer: Joel G Pickar

Reviewer’s report:

MAJOR COMPULSORY REVISIONS (which the author must respond to before a decision on publication can be reached)

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)

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?

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.

4. P8 paragraph starting line 4: We used a translatory thrust spinal manipulation technique with the subject in a side-lying position (Figure 3). This technique is a classic high-velocity low-amplitude technique described by Hondras et al. [8] and others [29, 39]……

The manipulation used in this study, while having similarities to the classic HVLA manipulation described in reference 8, appears to have significant differences which are important to consider when interpreting the data. As the author’s imply but aren’t specific about, the intent of the classic HVLA manipulation is to isolate the manipulative force to specific segments. This was achieved in reference 8 by placing the manipulative hand directly over the segment where the isolation or localization was desired. In Hondras’s study, the contacting hand was placed over the sacroiliac joint or a specific lumbar segment. In the present study the thrusting hand appears to have been placed on the pelvis not on the lumbar spine. In the present study, the manipulation, if indeed it manipulated the lumbar spine rather than the pelvis, represents a long lever rotary maneuver (not translatory as stated in the first sentence) applied in a non-localized manner to the lumbar spine. If the author’s maintain that a lumbar segment was localized or isolated, how was that segment chosen in the first place, was it the same in all participants, and how was the maneuver delivered to isolate those segments? In that 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.

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.
6. 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.

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?

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.

9. P 9 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.

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.

MINOR ESSENTIAL REVISIONS (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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.

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.

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?

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

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?

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.

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.

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

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 L14 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?

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.

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.

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.

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.

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.

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.

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).

27. P8 line 17: subjects factor: patient group; audible response group)

Factor should be plural in that two factors were analyzed.

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”.

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.

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.

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].
Studies directly relevant to the lumbar spine show no increase in spindle sensitivity with low back pain or noxious stimulation of paraspinal tissues.
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 26: 1528-1536, 2001
These studies should be presented here. (also see comment regarding P3 Lines 14-18)

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.

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

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.

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.

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.

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.

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

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)

DISCRETIONARY REVISIONS (which are recommendations for improvement but which the author can choose to ignore)

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.

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.

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.

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.

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.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.