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Development of an Experimental Model of *In Vivo* Cervical Facet Joint Loading and Capsule Distraction

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This paper has not been screened for accuracy nor refereed by any body of scientific peers and should not be referenced in the open literature.

ABSTRACT

While much research points to mechanical injury of the cervical facet joint and its capsular ligament as a likely mechanism for whiplash injury, findings remain speculative for the potential of such injuries to initiate and/or maintain pain. Mechanical injury of the cervical facet joint has been suggested during whiplash kinematics in experimental studies. However, determining a relationship between these mechanical conditions and pain requires simultaneous incorporation of controlled injury conditions, relevant biomechanical measurements, and methods for evaluating physiologic and clinical outcomes of pain. Therefore, this study presents the development of such an in vivo model in the rat. To this end, we provide a summary of preliminary findings characterizing the relationship between facet joint distraction and pain symptoms. A newly developed model of in vivo facet joint loading using controlled distraction across the C6/C7 joint is presented. Preliminary findings of a common clinical measure of behavioral hypersensitivity (mechanical allodynia) are presented as a quantifiable gauge of pain symptoms for imposed facet injury. In addition to data supporting the accuracy, reproducibility, and validity of these methods, preliminary biomechanical data are provided to quantify facet joint injury in the context of associated behavioral outcomes for long-term outcome studies. Pilot findings with this model of facet distraction point to the cervical facet capsule's ability to produce pain symptoms. Results provide a mechanical context for facet joint injury as a mechanism of pain and suggest this in vivo model may be a useful tool for examining neck pain associated with whiplash injuries and for characterizing injury mechanisms leading to these syndromes.

INTRODUCTION

Chronic pain, of which neck pain comprises nearly 30% of cases, has an estimated annual cost of $90 billion for treatment and work loss (Freeman et al., 1999). In addition, many pain syndromes in the spine remain intractable to treatment, adding to the challenge in managing painful neck injuries. Whiplash injuries and their associated disorders often lead to neck pain and are a widespread problem in today's society, with an estimated incidence of 4 per 1000 population (Barnsley et al., 1994). As many as 42% of whiplash injuries become chronic, with chronic pain persisting in an estimated 10% of cases (Barnsley et al.,

1994). Despite the high incidence of whiplash-associated neck pain, little remains known about the injuries producing these syndromes and the physiologic mechanisms responsible for their persistence.

Clinical and epidemiological studies point to the cervical facet joint as a likely candidate for pain generation due to its mechanical loading during whiplash-related injury (Aprill and Bogduk, 1992; Barnsley et al., 1993, 1994; Bogduk and Marsland, 1988; Grauer et al., 1997; Lord et al., 1996; Luan et al., 2000; Ono et al., 1997; Panjabi et al., 1998a, 1998b; Siegmund et al., 2001; Winkelstein et al., 2000; Yoganandan and Pintar, 1997; Yoganandan et al., 1998). Clinical studies of patients reporting painful neck injury have identified the facet joint as the site of pain in 25-62% of cases (Aprill and Bogduk, 1992; Barnsley et al., 1994), with the C5-C7 spinal levels being the most commonly injured in whiplash (Barnsley et al., 1995; Bogduk and Marsland, 1998). Histologic studies of rabbit, rat, and cadaveric human tissue have identified nociceptive nerve fibers throughout the structures of the facet joint, including the capsular ligament (capsule) (Cavanaugh et al., 1996; Giles and Harvey, 1987; Inami et al., 2001; McLain, 1994; Ohtori et al., 2001). These studies imply that neural input from the facet joint due to loading of its vertebrae or any of its soft tissue elements has the potential for initiating and/or modulating pain sensation. Moreover, anesthetic nerve blocks of painful facet joints offer relief to patients with both general neck pain and whiplash-induced neck pain, suggesting a role for this joint as a pain source (Barnsley et al., 1993; Bogduk and Marsland, 1988; Lord et al., 1996).

Biomechanical studies also provide support for a mechanical role of the facet joint in whiplash injury. "Abnormal" motions in the cervical spine have been hypothesized as mechanisms of whiplash injury (Grauer et al., 1997; Kaneoka et al., 1999; Luan et al., 2000; Ono et al., 1997; Yoganandan et al., 2002), and these kinematic patterns include hyperextension of the lower cervical spine, facet joint impingement, synovial fold pinching, and facet capsule stretch (Grauer et al., 1997; Luan et al., 2000; Ono et al., 1997; Panjabi et al., 1998a, 1998b; Pearson et al. 2004; Siegmund et al., 2001; Winkelstein et al., 2000; Yoganandan and Pintar, 1997; Yoganandan et al., 1998). Also, in isolated cadaveric mechanical studies of the facet capsule in flexion, extension, and combined bending and shear, the capsule has been shown to be at risk for subcatastrophic injury for vertebral motions occurring during low-velocity impacts, further implicating the capsule in whiplash-initiated pain (Siegmund et al., 2001; Winkelstein et al., 2000). However, despite the abundance of evidence suggesting involvement of the facet joint and its capsule in whiplash injury and neck pain, no studies have specifically investigated the role of facet-mediated injury in neck pain generation and/or maintenance.

Rodent pain models provide useful tools for examining painful injuries, with particular utility in linking nociceptive and physiologic responses to behavioral outcomes. For example, in low back pain models, behavioral hypersensitivity is commonly measured by mechanical allodynia (an increased sensitivity to a non-noxious stimulus), observed in the dermatome of the injured neural tissue (Colburn et al., 1999; Hashizume et al., 2000). Allodynia is measured by the frequency of paw withdrawals elicited by stimulation with otherwise non-noxious von Frey filaments (Hashizume et al., 2000) and is a useful behavioral outcome as it is also representative of clinical symptoms observed in chronic pain patients and provides a gauge of nociceptive responses (Barlas et al., 2000; Ochoa, 2003; Sheather-Reid and Cohen, 1998). In the rat, the same spinal nerves that innervate the lower cervical spine also innervate the shoulder and forepaw (Takahashi and Nakajima, 1996), allowing for the measurement of forepaw allodynia as an indicator of increased behavioral sensitivity after facet joint injury.

Therefore, the goal of this study was to develop a repeatable *in vivo* rat model of controlled mechanically-induced painful facet joint distraction. This study presents a novel rodent facet distraction model, with subsequent pain responses for C6/C7 tensile facet distraction. The effect of joint distraction magnitude was examined in the context of resulting behavioral hypersensitivity, as measured by forepaw mechanical allodynia. These preliminary efforts provide an early basis for simultaneous investigation of the biomechanics of whiplash injuries with physiologic mechanisms of nociception and pain.

METHODS

All experimental procedures have been approved by the University of Pennsylvania Institutional Animal Care and Use Committee (IACUC). Experiments were performed using male Holtzman rats, weighing 325-375 grams at the start of the study. Animals were housed under USDA & AAALAC-approved conditions with free access to food and water.

Surgical Procedure & Tensile Facet Injury

All procedures were performed under inhalation anesthesia (4% halothane for induction, 2.5% for maintenance). Rats were placed in a prone position and the paraspinal musculature cleared from C4-T2. The laminae, facet joints and spinous processes at C6/C7 were exposed bilaterally under a surgical microscope (Carl Zeiss, Inc., Thornwood, NY) and the interspinous ligament and ligamentum flavum were minimally resected at C6/C7 to facilitate joint distraction. A customized loading device was used to apply quasistatic tensile distraction and return of the C6/C7 facet joint and its capsule (Figure 1). Briefly, two sets of microforceps were rigidly attached to the C6 and C7 spinous processes, fixing the C7 vertebra in place while allowing for translation of the C6 vertebra using a manual micrometer (Newport Corp., Irvine, CA). The micrometer was rigidly coupled to the C6 microforceps and interfaced with a linear variable differential transducer (LVDT) (MicroStrain, Inc., Williston, VT; resolution = 0.16 μm) that recorded forceps displacements at 10 Hz.

Each rat received one of the following procedures: (1) tensile joint *distraction* (n=8), or (2) *sham* (device attachment only) (n=4). For the *distraction* procedure, the C6 vertebra was translated rostrally, held for 30 seconds, and returned to its initial position, unloading the joint. *Sham* surgeries consisted of device attachment only, for the same duration as the distraction group.

Prior to distraction, acrylic black paint marks (diameter=0.36±0.20 mm) were applied to the right C6 and C7 laminae, to allow for motion tracking (Figure 2). During distraction, the exposure and right facet joint were imaged at 5 fps using a digital video camera (Pixera Corp., Los Gatos, CA) with 640 x 480 pixel resolution, and all data acquisition was synchronized in time. After each procedure, wounds were closed with silk suture and surgical staples. Rats were allowed to recover in room air and were monitored during recovery.

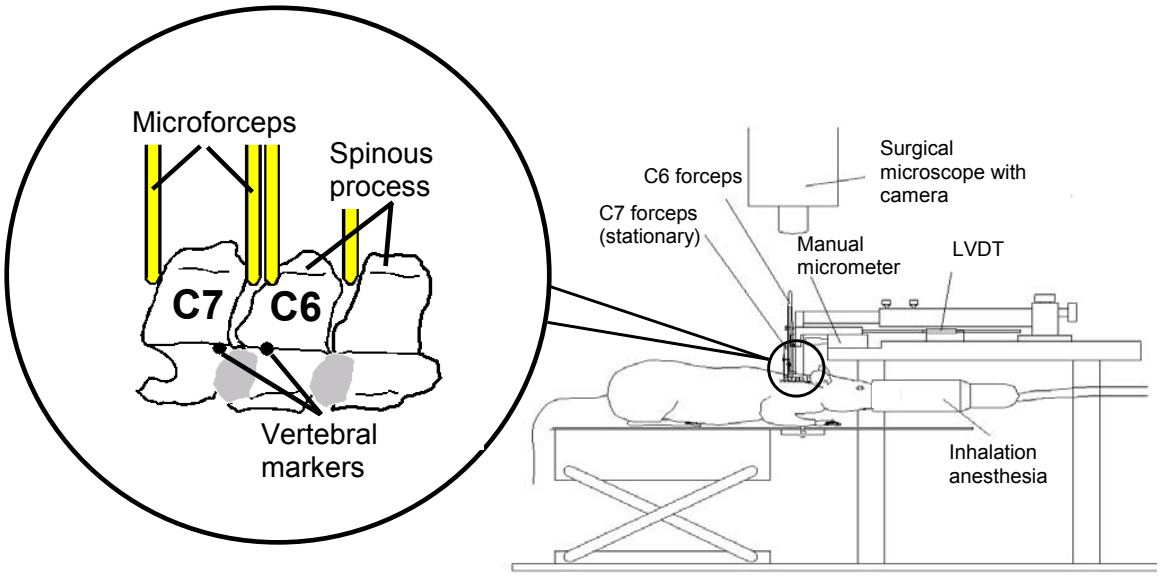

Figure 1: Schematic showing surgical setup, with forceps, micrometer, and LVDT. A surgical microscope is mounted above the distraction device for image analysis. The inset picture (left) illustrates the relative placement of microforceps on the C6 and C7 spinous processes. For the tensile distraction protocol used in this study, the C7 spinous process is rigidly held in place while the C6 spinous process is displaced in the rostral direction.

Image Analysis

Imposed *in vivo* facet distraction was calculated using the C6 and C7 vertebral markers. Each pair of markers was digitized using Scion Image software (Scion Corp., Frederick, MD), and the centroid of each marker calculated in its initial configuration as well as at maximal distraction. Vertebral distractions in both the horizontal (x-axis) and vertical (y-axis) directions were obtained by subtracting the initial centroid coordinates from those at maximal distraction (Figure 2). To confirm that distraction was being applied along the x-axis, spinal rotation angles were calculated as the change in orientation, relative to the horizontal axis (x-axis), of the line segment connecting the C6 and C7 vertebral marker centroids (Figure 2). These angles were used as a measure of the loading vector and degree of symmetry of the applied tensile distraction.

Behavioral Testing

All rats were evaluated for forepaw mechanical allodynia on days 1, 3, 5, 7, 10, 14, 21, 28, 35, and 42, postoperatively. Allodynia was measured as the number of forepaw withdrawals elicited by a defined non-noxious mechanical stimulus and was measured for both forepaws of each rat. Prior to surgery, animals were acclimated to the testing environment and tester and baseline measurements were recorded. The baseline measurements of allodynia were negligible, indicating the stimulus was indeed non-noxious. The same tester, who was blinded to the surgical procedure, performed all behavioral testing for this study. Behavioral testing methods used here for forepaw sensitivity have been previously used in cervical pain models (Hubbard and Winkelstein, 2004; Lee et al., 2004). Briefly, in each testing session, rats were subjected to 3 rounds, separated by 10 minutes each, of 10 tactile stimulations to the plantar surface of each forepaw using 2 and 4 gram von Frey filaments (Stoelting Co., Wood Dale, IL). A positive response was counted when the rat emphatically lifted its paw upon stimulation, which was often accompanied by licking or tightening of the paw.

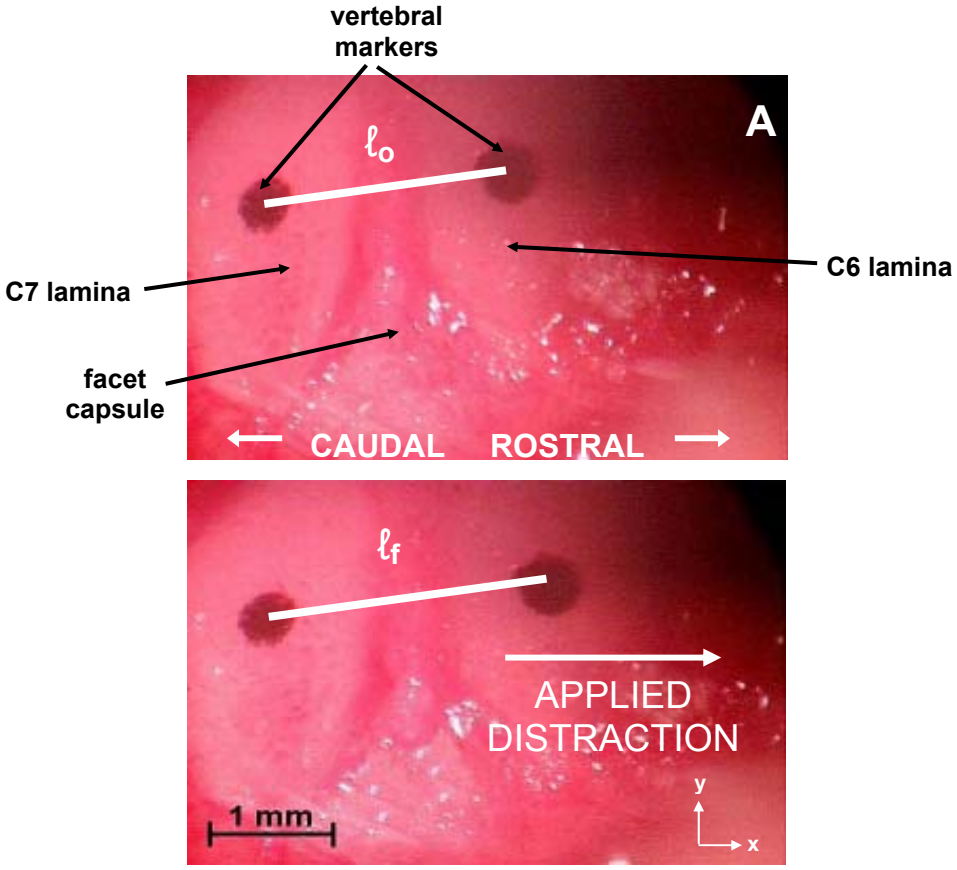

Figure 2: Representative *in vivo* images of the initial position (A) and at maximal distraction (B) of the facet joint. Also shown are the vertebral markers on the C6 and C7 laminae and the corresponding distance between the markers (ℓ_o, ℓ_f) used to calculate vertebral distraction.

Statistical Analysis

For both groups (*distraction, sham*), allodynia responses in the right and left forepaws were compared using a paired t-test. To compare mechanical allodynia after *distraction* and *sham* procedures, a Student's t-test was used. All statistical analyses were performed using SYSTAT (SYSTAT Software Inc., Richmond, CA) and significance was defined as $p<0.05$.

RESULTS

During loading, no observable damage of the facet joint or its capsule was observed. Also, at the completion of the study, examination of the facet capsule under a surgical microscope indicated no gross mechanical injury in any of the animals. After surgery, all rats demonstrated normal functioning with grooming and consistent weight gain. They showed good head mobility, indicating that there were no adverse effects of the procedures on neck mobility.

For animals in the *distraction* group, forceps displacement was obtained from LVDT data (Figure 3) and vertebral marker displacement from digitized images (Table 1, Figure 2). Digitization error in locating vertebral markers was small (0.004±0.005 mm) compared to imposed distractions. The mean applied distractions in the x- and y-directions were 0.53±0.16 mm and 0.08±0.11 mm, respectively (Table 1). The mean applied loading rate was 0.08±0.03 mm/s, while the mean spinal rotation angle was 2.3±1.7° (Table 1).

Mechanical allodynia was not significantly different between the left and right forepaws for either *distraction* or *sham* groups for testing with both the 4 g filament ($p>0.12$ and $p>0.06$, respectively) (Figure 4) and the 2 g filament ($p>0.06$ and $p>0.18$, respectively) (data not shown). As such, left and right allodynia responses for each rat were averaged for analysis between groups. Within the *distraction* group, allodynia was immediately increased over baseline on day 1, with a slight decrease over time (Figure 5). Allodynia in the *distraction* group was significantly elevated over *sham* ($p<0.007$, 2 g; $p<0.003$, 4 g) for 10 days following injury and generally elevated above *sham* values for the remainder of the evaluation period (Figure 5). *Sham* responses were low and not different from baseline values.

Total mechanical allodynia over the entire postoperative period was calculated for each animal as a measure of cumulative hypersensitivity. Total allodynia for the *distraction* group (39.7±11.5 responses) was significantly greater than for *sham* (8.6±0.9 responses) ($p<0.0005$) for testing with the 4 g von Frey filament (Table 1). The same trends were observed for testing with the 2 g filament (data not shown), with *distraction* significantly elevated over *sham* ($p<0.0005$).

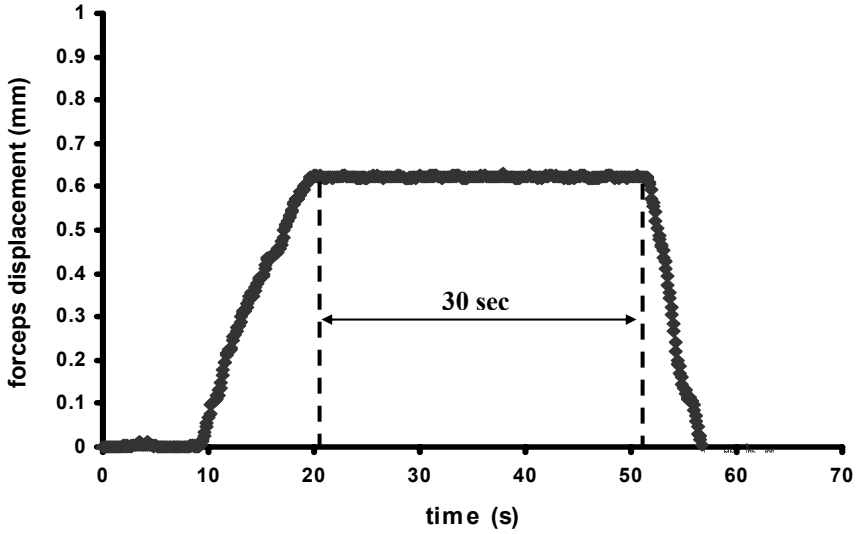

Figure 3: Representative C6 microforceps displacement data during the distraction sequence, as measured by the LVDT.

Table 1. Summary Of Imposed Facet Joint Distraction Mechanics And Resultant Allodynia.

Group	Rat #	Weight (g)	Vertebral distraction (x) (mm)	Vertebral distraction (y) (mm)	Spinal rotation angle (°)	Total allodynia (through day 14, 4g von Frey)
DISTRACTION	L2	334	0.53	-0.19	-2.56	28.5
	L5	370	0.65	-0.17	-4.67	62.5
	L6	332	0.70	-0.13	0.41	47.5
	L7	352	0.34	-0.09	2.86	25.5
	L9	332	0.60	0.07	0.80	39
	L14	360	0.38	-0.01	3.80	38.5
	L17	354	0.33	0.07	-3.31	37
	L22	364	0.69	-0.19	0.01	39
AVG ± S.D.		**350 ± 15**	**0.53 ± 0.16**	**-0.08 ± 0.11**	**2.30 ±1.70**	**39.7 ± 11.5**
SHAM	L3	342	-	-	-	7.5
	L16	356	-	-	-	8.5
	L24	328	-	-	-	9
	L30	358	-	-	-	9.5
AVG ± S.D.		**346 ± 14**	**-**	**-**	**-**	**8.6 ± 0.9**

CONCLUSIONS

This study offers preliminary evidence of a relationship between controlled facet joint distraction and behavioral outcomes suggestive of pain symptoms. The results of this study demonstrate that mechanical allodynia is produced in the forepaw following tensile distraction of the C6/C7 facet joint and that this behavioral sensitivity is maintained over time, implicating the facet joint in painful neck injuries.

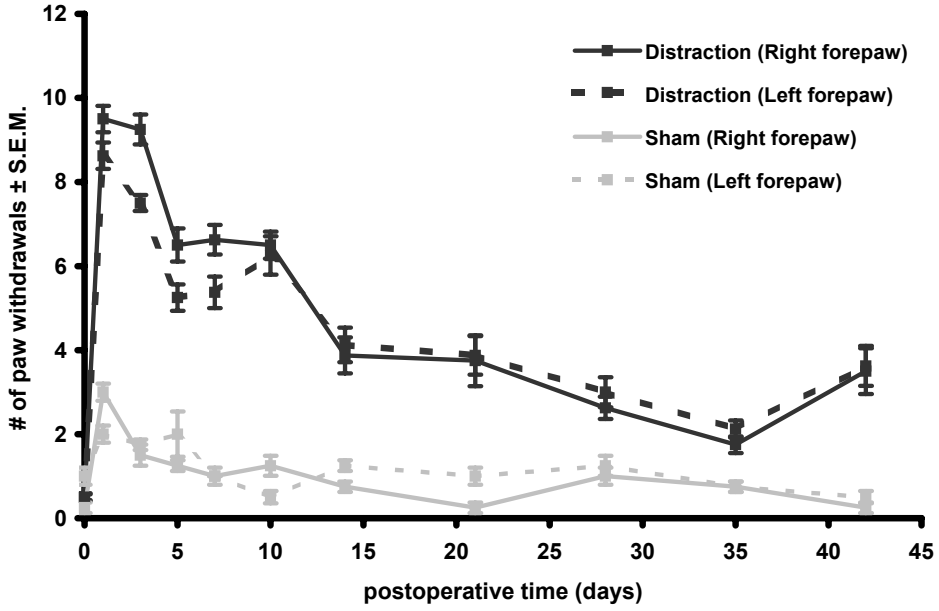

Figure 4: Mechanical allodynia as measured by the number of paw withdrawals in the right and left forepaws for *distraction* and *sham* procedures using the 4 g von Frey filament. There was no significant difference in allodynia between the forepaws for either procedure at any postoperative timepoint.

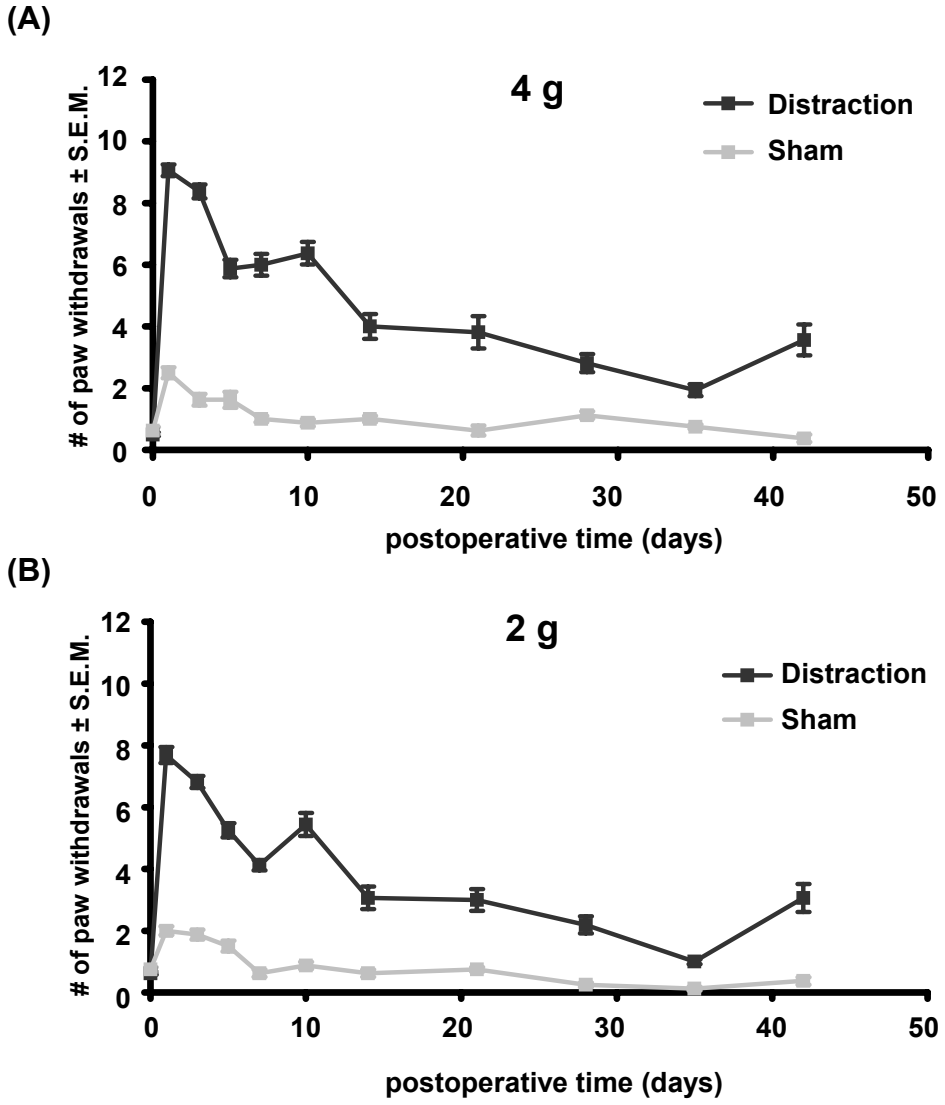

Figure 5: Average mechanical allodynia as measured by the number of paw withdrawals for *distraction* and *sham* procedures. The *distraction* procedure produced significantly increased allodynia above *sham* ($p<0.003$) that was maintained for 10 postoperative days, for testing with the 4 g filament (**A**). Results were similar for testing with the 2 g von Frey filament, with allodynia for distraction significantly elevated above sham ($p<0.007$) (**B**).

The facet joint distraction device presented here provides utility for applying controlled and repeatable facet joint distraction, with control of mechanical injury parameters, such as distraction magnitude, rate, and hold duration. The imposed joint injury was primarily tensile in nature, with little off-axis rotation. Off-axis rotation angles were small (2.3±1.7°), confirming that joint distraction was symmetric about the spinal axis and aligned with the rostral-caudal direction. The lack of difference in allodynia responses between the right and left forepaws within both groups offers further evidence supporting the application of a symmetric injury. In addition, it should be noted that the *sham* procedure involved the same ligament resection and device attachment as that of the *distraction* group. Allodynia responses following *sham* procedures were not different from baseline values (Figure 5), suggesting that the tensile distraction of this joint is necessary to produce pain responses.

The use of an *in vivo* model allows the simultaneous investigation of joint mechanics and pain symptoms. In particular, a close examination of mechanical data from three weight-matched rats in the *distraction* group (L2, L6, L9) (Table 1) suggests there may be a relationship between applied vertebral

distraction and resultant total allodynia. Data from these rats reveal an increase in total allodynia for increasing vertebral distraction, which suggests a distraction threshold may exist, above which pain symptoms are produced. In addition, these *in vivo* data can be interpreted in the context of existing cadaveric data by scaling the imposed vertebral distractions by the original distance between the C6 and C7 vertebral markers to create a normalized measure of distraction across the vertebrae. In the current study, the average normalized distraction was 29.4±2.5%, which is comparable to strain values observed across the facet capsule during cadaveric whiplash simulations. Panjabi et al. (1998b) and Pearson et al. (2004) reported peak facet capsule strains ranging between 29.5-39.9% at the C6/C7 joint level for 6.5, 8, and 10.5 G accelerations, using mini-sled tests of human cadaveric head-neck specimens. In addition, Winkelstein et al. (2000) reported mean subcatastrophic failure capsule strains as low as 35% in tension for isolated cadaveric cervical motion segments. For these subcatastrophic failures, the facet capsule remained grossly intact, but mechanical data suggested microscopic failures might have occurred. Taken together with the findings of the current study, these data suggest that under whiplash-like loading conditions, pain symptoms may be produced. Likewise, the cadaveric data provide mechanical context suggesting that subcatastrophic injuries to the capsular ligament may be produced in this animal model, requiring further investigation.

While many clinical and biomechanical studies have implicated the facet joint in neck pain, this study utilizes an *in vivo* model to provide preliminary evidence of a direct role for the joint in eliciting neck pain by demonstrating behavioral hypersensitivities after joint distraction. In previous studies using animal models of low back pain, mechanical allodynia has been correlated with and is hypothesized to be due to a host of physiologic changes in the central nervous system, including neuronal plasticity, glial cell activation and cytokine upregulation (DeLeo and Yezierski, 2001; Hashizume et al., 2000; Ji and Woolf, 2001; Rutkowski et al., 2002; Sweitzer et al., 1999; Watkins et al., 1995; Winkelstein et al., 2001b). In addition, electrophysiologic studies have demonstrated altered neurophysiology resulting from loading of the lumbar facet joint and its capsule (Avramov et al., 1992; Cavanaugh et al., 1996). Together, these physiologic changes contribute to central sensitization and persistent pain. Indeed, in clinical research, central sensitization has been hypothesized as a mechanism of chronic pain after whiplash injury (Barlas et al., 2000; Curatolo et al., 2001; Kivioja et al., 2001). The results presented here demonstrate increased allodynia after facet joint distraction and further support a role for the facet joint in neck pain.

This model of facet joint-mediated behavioral hypersensitivity can be a useful tool to further investigate the relationship between tensile facet joint distraction and pain. While this study has explicitly examined and quantified joint distraction mechanics in the context of pain symptoms, it is recognized that the scenarios imposed may also load additional spinal structures, including the nerve root and intervertebral disc, due to bending in the sagittal plane. Because injury to such structures may also contribute to neck pain, additional efforts are needed to characterize the associated tissue loading in this model. Additionally, efforts are also needed to determine an appropriate scaling factor between the rat and human, for accurate comparison of mechanical data. Nonetheless, the model presented here provides a controlled paradigm for examining the physiologic effect of several facet joint injury parameters (i.e. loading rate, magnitude, and/or duration), and as such, offers a novel link between cervical facet joint biomechanics and resultant physiology.

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DISCUSSION

PAPER: **Development of an Experimental Model of In Vivo Cervical Facet Joint Loading and Capsule Distraction**

PRESENTER: ***Kathryn Lee, Department of Bioengineering, University of Pennsylvania***

QUESTION: *Erik Takhounts, NHTSA*
Are you trying to address the possible mechanism with whiplash injuries? Is that what the research is oriented towards? Did I understand it correctly?

ANSWER: This is actually not a whiplash model. This is more of trying to understand the mechanism so some of the literature suggests that the capsule undergoes stretch during whiplash scenarios and some of the electrophysiologic studies have shown that stretching of the capsule elicits these nonsusceptive electrical changes. And so, we're sort of looking at some of the other pain symptoms that we may be able to get out of this capsule stretch. So we're actually not trying to, necessarily, model whiplash but rather look at some of the mechanisms.

Q: One of the features of whiplash injuries is that it happens at relatively low rates of loading. And the other one, it sometimes manifests itself after a period of time has passed and then the pain sort of occurs. Your model shows that the pain subsides with time, sort of the opposite trend. Do you have any explanation for that?

A: Well actually, if we consider the average lifespan of the rat, which is just about a year, the existence of these sensitivities for two weeks is actually, could be a chronic state.

Q: Oh. Okay. Thank you.

A: No problem.

QUESTION: *Guy Nusholtz, DaimlerChrysler*
Have you thought of trying to measure the electrical activity that's coming out or after a period of time, sacrifice the rat and see what type of physiological changes you got? Is that going to be part of your extended program?

A: Sure. The first question: Have we been interested in looking at some of this electrical activity? We are interested in looking at it. We're working with a rat model so we can look at some of these behaviors, but it's a little difficult right now with the set-up that we have to imagine doing electrophysiology in such a small working space. I think the area of the rat capsule is about 2 mm x 2 mm. And so, I know that some of the other animal models that look at this electrophysiology do it in larger animals. So at some point, that may be an option. And, have we looked at some of the physiologic changes? Actually, some of the work that Beth is going to present later on this week will show that we looked at some glial cell activation in the spinal cords. We looked at some of the central changes and actually found that there was increased activation of astrocytes in this distraction model.

Q: I guess the question is: You're going to move the sets. You're going to move the two vertebrae differentially. Is this a response of the neurological system without any pathology, or is it actually something physical that's occurred? So, the question is: Is there any real physiological damage that occurred?

A: Yeah. We would be very interested in looking at it. This is a work-in-progress so we're not quite at that point yet, but that's definitely some place that we want to go with this.

Q: Okay. Thank you.

A: No problem.

QUESTION: *Andre Loyd, Duke University*
Can you explain what paw withdrawal has to do with pain?

A: Sure. It's the same nerves that innervate the facet joint and its capsule in the neck also extend down. So, clinically there may be symptoms of sensitivity that are removed from the site of injury. And so, the dermatome of the C7 spinal nerve—C6/7 that we're looking at—extends down and actually innervates the forepaw. We do see sensitivity in the forepaw that can be representative of some sort of sensitivity that's also going on in the neck.

Q: And the second question: Can you explain how you physically connected the microforcepts to the vertebral bodies?

A: We connected them to the spinous process, so the spinous process was slightly elevated. If the spinous process is like this, we just took the microforcepts and we had a screw attached onto them so we could place them around the spinous processes and then screw them in pretty tight.

Q: Thanks.

A: Um hm.

QUESTION: *Frank Pintar, Medical College of Wisconsin*
I think this is a great start to understanding pain and mechanics and stretch. I think that using strain as an input is a good start. Maybe I didn't understand your stretch model right, but how do you know that the pain is actually coming from the sets as opposed to the DRG or some other area?

A: And when I mentioned that we're not exactly sure what this model is doing to other structures, we do have a nerve root compression model in the lab; and that involves compressing the nerve root around the DRG with micro vascular clips and looking at some of the same behavioral changes. And, we actually see a greater degree of allodynia after that so we're pretty sure that we're not imposing that degree of injury to the nerve roots, but there is definitely room for some sort of affect on the nerve root or the disk so that's where we'd like to go next to figure out what's going on.

Q: Would it make sense to do any, another control where you actually just try to do damage to that part of the capsule as opposed to stretching the whole thing? Like, severing the capsule or something like that? Does that work?

A: Yeah. That would be interesting. We haven't tried that, but that's something that would be interesting to see what the changes are after that.

Q: Okay. Thank you.