Whole Body Vibration Induces Forepaw and Hind Paw Behavioral Sensitivity in the Rat

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ABSTRACT: Whole body vibration (WBV) has been linked to neck and back pain, but the biomechanical and physiological mechanisms responsible for its development and maintenance are unknown. A rodent model of WBV was developed in which rats were exposed to different WBV paradigms, either daily for 7 consecutive days (repeated WBV) or two single exposures at Day 0 and 7 (intermittent WBV). Each WBV session lasted for 30 min and was imposed at a frequency of 15 Hz and RMS platform acceleration of 0.56 ± 0.07 g. Changes in the withdrawal response of the forepaw and hind paw were measured, and were used to characterize the onset and maintenance of behavioral sensitivity. Accelerations and displacements of the rat and deformations in the cervical and lumbar spines were measured during WBV to provide mechanical context for the exposures. A decrease in withdrawal threshold was induced at 1 day after the first exposure in both the hind paw and forepaw. Repeated WBV exhibited a sustained reduction in withdrawal threshold in both paws and intermittent WBV induced a sustained response only in the forepaw. Cervical deformations were significantly elevated which may explain the more robust forepaw response. Findings suggest that a WBV exposure leads to behavioral sensitivity. © 2013 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 31:1739–1744, 2013

Keywords: whole body vibration; spine; pain; injury

Several epidemiological studies have linked exposure to whole body vibration (WBV) with neck and back pain,[1–4] suggesting that vibration can lead to the onset of both pain syndromes. American male workers operating vibrating vehicles, such as industrial trucks and tractors, have been reported to have a higher prevalence of low back pain and are three-times more susceptible to acute herniated lumbar discs than workers whose occupations do not involve such exposures.[3,5] Also, military helicopter aviators report increased pain during deployment compared to their pre-deployment reports of pain, with between 22–37% reporting neck and 39–70% reporting low back pain.[4] Further, the frequency of pain was significantly higher for aviators who experienced substantially increased flight hours during deployment compared to those who did not,[4] suggesting that the amount of exposure to WBV may affect the pain.[4] Despite the strong suggestive evidence of these epidemiological studies that pain can develop from WBV and may be influenced by the nature and frequency of the exposure, there is still little known about how these factors relate to the onset, maintenance, and resolution of pain.

A limited number of studies have defined the biomechanical response to vibration and related resonance and vibration frequency to physiological responses known to be involved in pain-related injuries. The resonant frequency of the seated human undergoing vertical vibration has been reported to be 4.5 Hz from a series of studies using accelerometers on the first and third lumbar vertebrae (L1, L3) and the sacrum of volunteers exposed to vertical vibrations, ranging in frequencies from 2 to 15 Hz.[6] A later study using similarly seated human volunteers, with accelerometers placed on L3 and vertical vibration frequencies ranging from 0.2 to 20 Hz with varying magnitudes also reported a primary resonance of 4–6 Hz, with a secondary resonance between 8 and 12 Hz.[7] Interestingly, the resonant frequency of the prone rabbit exposed to horizontal vibration between 2 and 8 Hz also was approximately 4.5 Hz.[8] In contrast, the resonance of the seated primate in the vertical direction ranges from 9 to 15 Hz.[9] In addition to these biomechanical studies, studies have reported changes in pain-related neuropeptides and damage to arterial endothelial cells for WBV exposures ranging from 4.5 to 60 Hz.[8,10] Although all of these studies suggest WBV as a putative mechanism to induce pain and provide important mechanical and physiological context for that hypothesis, the relationship between WBV and pain still remains speculative.

The objective of this study was to develop an in vivo model of WBV in the rat, and to evaluate pain responses for two different vibration exposure paradigms, investigating the relative effects of an only intermittent exposure and a repeated daily exposure. Based on prior transmissibility studies,[7–10] each WBV exposure was applied at a frequency of 15 Hz for 30 min. The effect of each WBV exposure was measured in the context of the onset and/or maintenance of behavioral sensitivity, using alterations in the paw withdrawal responses for the forepaw and hind paw. To provide mechanical and anatomical regional context for behavioral responses between exposure groups, the deformations in the cervical and lumbar regions of the rat during each WBV exposure were also measured to quantify the compression and extension in each region.

METHODS

All procedures were approved by the University of Pennsylvania the Institutional Animal Care and Use

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Committee and performed in accordance with the Committee for Research and Ethical Issues of the International Association for the Study of Pain.[11] Experiments were performed using male Holtzman rats (weighing 280–360 g at the start of the study), housed under conditions approved by the United States Department of Agriculture and the Association for Assessment and Accreditation of Laboratory Animal Care International, with a 12–12 h light–dark cycle and free access to food and water.

Vibration exposure was performed under inhalation anesthesia (4% isoflurane for induction, 3.5% for maintenance). Separate groups of rats underwent a whole body vibration either daily for 7 consecutive days starting on Day 0 (*repeated WBV*; $n = 6$) or two single exposures of vibration at Day 0 and again on Day 7 (*intermittent WBV*; $n = 8$; Fig. 1). A control group (*sham*; $n = 4$) underwent anesthesia exposure according to the timing and scheduling used in the *repeated WBV* group (Fig. 1). For each session of vibration exposure, after anesthesia was induced the rat was placed in the prone position on an acrylic platform that was vibrated in the horizontal ($x-$) direction at 15 Hz, with a peak-to-peak magnitude of 1.5 mm for 30 min, secured to the platform by velcro straps (Fig. 2). The platform was rigidly fixed to a linear servomotor (MX80L; Parker Hannefin; Cleveland, OH) controlled by a digital driver (VIX500IH; Parker Hannefin). A laser displacement sensor (LTC-050-10; MTI; 1.25 μm/mV) tracked the platform motion. Two miniature quartz shear accelerometers (ACC104A; Omega; 10 mV/G) measured the acceleration of each of the plate and the rat: one accelerometer was affixed to the moving plate and the other was embedded in a velcro strap secured to the lumbar region of the rat (Fig. 2). During WBV, black ink markings on the platform, the lumbar accelerometer, the lumbar velcro strap, and the stationary stage, as well as the eye itself, were tracked using a high speed CCD camera (VRI-MIROEX1-1024MM; Phantom; 640×480), to measure their respective displacements during each exposure session on Days 1 and 7 (Figs. 1 and 2). Accelerometer, imaging, and displacement data were each recorded at 120 Hz.

The accelerations and displacements of the plate and the rat were measured during WBV using the accelerometers and image markers in order to verify

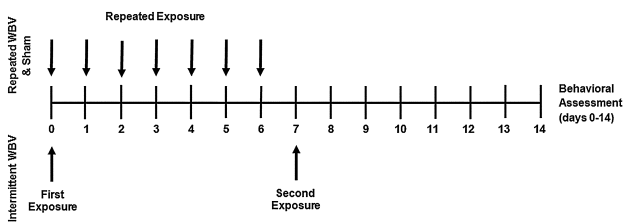

Figure 1. Schematic illustrating the timeline for exposures, rest periods, and daily behavioral assessment for the *repeated WBV*, *sham*, and *intermittent WBV* groups.

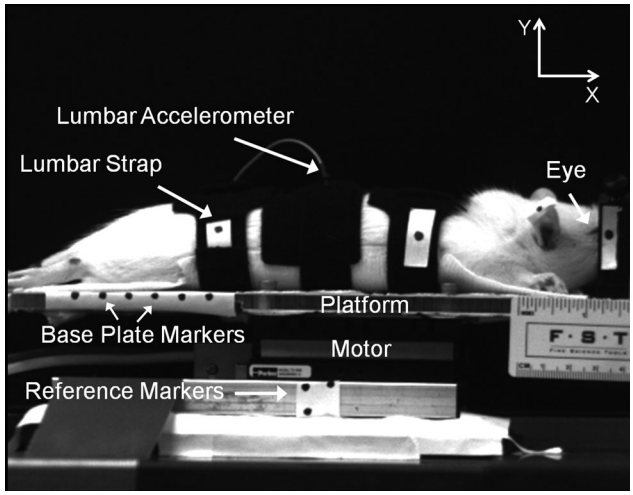

Figure 2. Image of the experimental setup showing the base plate, motor, lumbar accelerometer, and markers on the rat. The $x-$ (horizontal) and $y-$ (vertical) directions are also indicated.

that equivalent exposures were imposed and that similar kinematics were induced in the different groups. For each exposure, 15 min of the accelerometer data were used to determine the root mean square (RMS) acceleration for each of the plate and the rat, which were then averaged over all days of exposure for each rat. Similarly, 12 s of image data were taken to determine the displacements of the plate, the rat, the lumbar segment, and the eye (as a marker for the head), by digitizing their positions relative to the stationary reference markers in each image using ProAnalyst (Xcitex, Inc.; Cambridge, MA) (Fig. 2). Both sets of data were filtered using a 5th order Butterworth bandwidth filter. For each exposure, 15 min of displacement data were used to determine the mean peak-to-peak plate displacements, which were averaged over all exposure days for each rat. A repeated-measures ANOVA compared displacements and accelerations over the different exposure days and a one-way ANOVA compared the plate displacements and rat accelerations between groups.

The local two-dimensional deformations in each of the cervical and lumbar regions were determined in the sagittal plane (Fig. 2) during each WBV session using image data in order to estimate the extent of compression and/or extension. To do so, the vector lengths of the cervical region, taken between markers on the eye and the lumbar accelerometer, and of the lumbar region, defined between the lumbar accelerometer and the lumbar strap, were separately determined using the digitized positions from the images. The resting vector length for each region was defined as the length of the vector in the initial frame of the images, prior to any vibration. The maximum and minimum vector lengths also were calculated for each cycle of the WBV and the average maximum and minimum lengths were subtracted from the corresponding resting length for each rat to calculate the

change in vector length for each rat, separately for the cervical and the lumbar region. The accuracy in identifying and tracking the markers is 0.035 ± 0.054 mm. The error in measuring these vector lengths in this way is also small: 0.079 ± 0.046 mm for maximum vector length and 0.079 ± 0.039 mm for minimum vector length. Separate paired Student's *t*-test compared the change in lengths for the cervical and lumbar lengths.

Behavioral sensitivity was assessed by measuring the threshold for withdrawal in the bilateral forepaws and hind paws on all days in order to quantify the onset and maintenance of increased tactile sensitivity after procedures. Prior to any vibration exposure, rats were also assessed to provide a baseline measurement to serve as an unexposed control response for each rat. Methods to measure the paw withdrawal threshold were adapted from Chaplan's up/down method and have been previously reported and validated.[12–14] The response threshold was measured using increasing strengths of von Frey filaments (0.6, 1.4, 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, and 26.0 g-force), applied to the plantar surface of each paw. The lowest-strength filament to provoke a positive withdrawal response was taken as the response threshold if a positive withdrawal response was also validated by application of the next higher filament. Each testing session consisted of three rounds of five stimulations to each forepaw and hind paw, with at least a 10-min rest period separating each round. The positive responses of each rat for each of three rounds were recorded and averaged. The average forepaw and hind paw responses were separately averaged by group on each testing day. A repeated-measures ANOVA with Bonferroni correction compared temporal withdrawal thresholds between the *repeated WBV*, *intermittent WBV*, and *sham* groups. For the *intermittent WBV* group, a rate of recovery for each rat after an exposure was determined by calculating the best-fit line of the average withdrawal response, fitting the data after the first (Days 1–7) and second (Days 8–14) exposures (Fig. 1), separately for the forepaw and hind paw. A one-way ANOVA compared the rate of recovery between the two exposures for each of the paws, separately.

RESULTS

All rats demonstrated normal functioning with grooming and weight gain consistent with normal rats. The mean weight gain over the study period was 75 ± 18 g for the *repeated WBV* group, 97 ± 14 g for the *intermittent WBV* group, and 86 ± 25 g for the *sham* group, and was not different between groups. Rats that underwent either of the vibration exposure types showed normal mobility, with no adverse effects of the procedure.

Both the repeated and intermittent vibration groups were exposed to the same vibration profiles of the base plate. The mean RMS acceleration of the plate in the *repeated WBV* group was 5.79 ± 0.70 m/s^2 and 5.32 ± 0.67 m/s^2 in the *intermittent WBV* group, and was not significantly different from each other (Table 1). The mean horizontal displacement of the base plate also was not different between these two exposure groups: 1.93 ± 0.46 mm for the *repeated WBV* and 1.45 ± 0.25 mm for the *intermittent WBV* groups (Table 1). The mean RMS acceleration of the rats in the *repeated WBV* group was 6.18 ± 0.69 m/s^2 and 6.16 ± 1.01 m/s^2 in the *intermittent WBV* group (Table 1). Neither the acceleration of the plate nor the rat was significantly different between the two injury groups.

Table 1. Summary of Measured Accelerations and Displacements During Repeated and Intermittent WBV

WBV Group	Rat ID	Plate RMS Acceleration (m/s^2) ± SD	Rat RMS Acceleration (m/s^2) ± SD	Plate Displacement (mm) ± SD
Repeated WBV	1	6.26 ± 0.49	6.83 ± 0.34	2.24 ± 0.28
	2	6.28 ± 0.51	6.68 ± 0.07	2.23 ± 0.13
	3	6.34 ± 0.51	6.67 ± 0.18	2.49 ± 0.09
	4	6.08 ± 0.57	6.25 ± 0.68	1.82 ± 0.14
	12	4.87 ± 0.41	5.53 ± 1.14	1.40 ± 0.07
	13	4.93 ± 0.41	5.15 ± 0.73	1.42 ± 0.12
Repeated WBV, mean ± SD		5.79 ± 0.70	6.18 ± 0.69	1.93 ± 0.46
Intermittent WBV	36	4.93 ± 0.13	4.67 ± 0.42	1.27 ± 0.07
	37	4.67 ± 0.21	5.38 ± 0.00	1.20 ± 0.08
	38	4.74 ± 0.11	5.54 ± 0.18	1.24 ± 0.03
	39	4.67 ± 0.13	5.55 ± 0.68	1.24 ± 0.01
	40	5.30 ± 1.06	6.53 ± 1.14	1.45 ± 0.36
	41	6.07 ± 0.10	7.35 ± 0.73	1.72 ± 0.03
	42	6.08 ± 0.10	6.87 ± 0.42	1.75 ± 0.06
	43	6.13 ± 0.02	7.40 ± 0.00	1.72 ± 0.02
Intermittent WBV, mean ± SD		5.32 ± 0.67	6.16 ± 1.01	1.45 ± 0.25
WBV, mean ± SD		5.52 ± 0.70	6.17 ± 0.86	1.66 ± 0.44

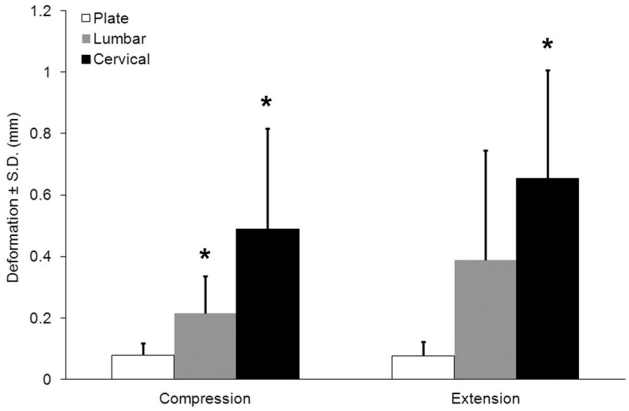

Figure 3. Compression and extension deformations in the cervical and lumbar regions during vibration exposure. The extent of compression in both the cervical and lumbar regions is significantly different than zero, while extension is only significant in the cervical region, as indicated by the asterisk (*). Also shown is the amount of deformation that was detected for the rigid plate during vibration, representing the small error associated with this method.

Deformations were induced in both the cervical and lumbar regions during vibration (Fig. 3). Both compression (0.215 ± 0.122 mm) and extension (0.388 ± 0.356 mm) were induced in the lumbar spine (Fig. 3), with the extent of compression being significant ($p = 0.019$), although extension was not significantly increased ($p = 0.064$). However, in the cervical region, the extent of both compression (0.490 ± 0.327 mm; $p = 0.032$) and extension (0.653 ± 0.352 mm; $p = 0.011$) was significant (Fig. 3).

Behavioral sensitivity was induced as early as Day 1 in both the hind paw and forepaw, regardless of the WBV exposure paradigm (Fig. 4). Specifically, the response threshold was significantly reduced in the hind paw at Day 1 after a single WBV exposure in both the *repeated WBV* ($p = 0.001$) and *intermittent WBV* ($p < 0.001$) groups (Fig. 4). However, only the *repeated WBV* exposure induced a decrease in threshold in the hind paw that was significantly lower ($p = 0.039$) than *sham* at all days (Fig. 4). In contrast, the response threshold remained at baseline levels at all time points following the *sham* exposure. The first vibration exposure in the *intermittent WBV* exposure paradigm induced only a transient decrease in withdrawal threshold in the hind paw that was significantly lower ($p = 0.004$) than baseline and was sustained through Day 5 (Fig. 4). Interestingly, when exposed to a second vibration (at Day 7), the resulting decrease in withdrawal threshold that was induced was sustained until Day 14 ($p = 0.039$), but did not decrease beyond withdrawal thresholds induced by the first exposure (Fig. 4).

Overall, both *repeated WBV* ($p < 0.0001$) and *intermittent WBV* ($p = 0.043$) induced significantly increased behavioral sensitivity in the forepaw compared to *sham* (Fig. 4). In fact, the behavioral sensitivity induced by *repeated WBV* was significantly lower ($p = 0.026$) than *intermittent WBV* (Fig. 4). The

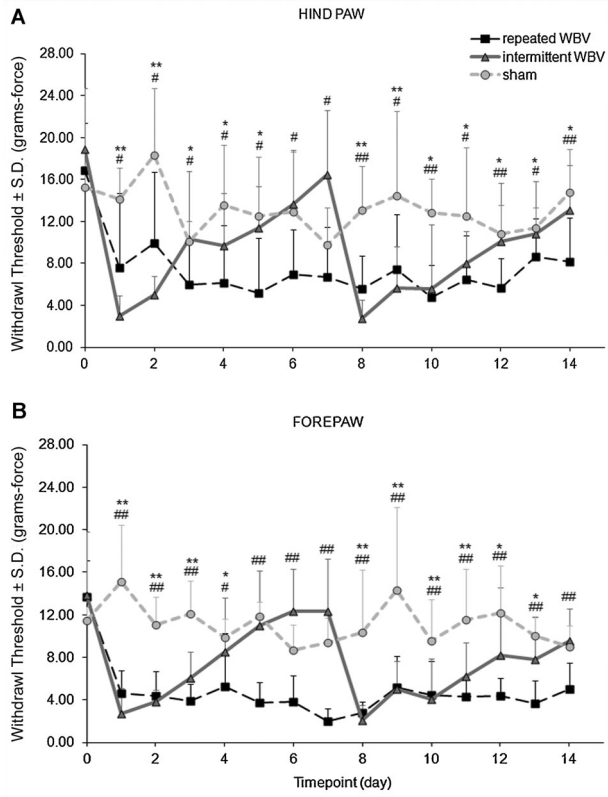

Figure 4. Withdrawal thresholds for *repeated WBV*, *intermittent WBV*, and *sham* groups in the forepaw and hind paw. A: The withdrawal threshold for the hind paw in the *repeated WBV* is significantly lower ($^{\#\#}p < 0.05$) than *sham* and baseline only on isolated days (Days 8, 10, 12, and 14), and is significantly lower ($^{\#}p < 0.04$) than only baseline on all other. *Intermittent WBV* is significantly lower ($^{**}p < 0.03$) than sham and baseline only on Days 1–2 and 8–9 and significantly lower ($^{*}p < 0.05$) than only baseline on Days 3–5 and 10–14. B: The threshold for forepaw withdrawal is significantly lower ($^{\#\#}p < 0.05$) in the *repeated WBV* group compared to *sham* and baseline on all days, except Day 4, but is significantly lower ($^{\#}p < 0.03$) than baseline on Day 4. *Intermittent WBV* is significantly ($^{**}p < 0.05$) different from *sham* and baseline on Days 1–3 and 8–11, and significantly different ($^{*}p < 0.05$) from baseline on Days 4, 12, and 13.

threshold for forepaw withdrawal was significantly lower ($p < 0.05$) in the *repeated WBV* group compared to *sham* on all days except Day 4, whereas *intermittent WBV* exposure was only different from *sham* on Days 1–3 and Days 8–11 (Fig. 4). Similar to the hind paw responses, *repeated WBV* exposure reduced ($p < 0.03$) the forepaw withdrawal threshold below baseline levels throughout the entire testing period regardless of whether during the loading or rest period (Fig. 4). *Intermittent WBV* exposure induced a reduction in withdrawal threshold in the forepaw that was transient, but for a shorter period than was observed in the hind paw, lasting only 4 days after the first exposure and 6 days after the second exposure (Fig. 4). The rate of recovery in the forepaw was significantly slower ($p = 0.036$) after the second vibration exposure (1.15 ± 0.39 g/day) than after the first exposure ($1.82 \pm .707$ g/day) (Fig. 4). In contrast, the rate of recovery was not different between the first and second exposure in the hind paw (Fig. 4).

DISCUSSION

This study demonstrates that even a single exposure of whole body vibration is sufficient to induce immediate and transient behavioral sensitivity in both the forepaw and hind paw, and that repeated exposure produces a sustained response (Fig. 4), substantiating WBV as a potential mechanism of producing pain. Although our in vivo pain model of whole body vibration in the rat appears to induce pain, there were no other adverse effects of the vibration, with all rats exhibiting normal weight gain consistent with that of naïve rats over a typical 14 day period. Neither the acceleration of the vibrating plate (5.52 ± 0.70 m/s^2; 0.56 ± 0.07 g) nor of the rat (6.17 ± 1.01 m/s^2; 0.63 ± 0.09 g) were different between groups in our study. Of note, control of the rat acceleration was the primary goal in establishing this new model. Nonetheless, both of these values fall in the range of the acceleration magnitudes used in other transmissibility studies using both humans and other species, which range from 0.1 to 5 g[7–10]; the 15 Hz vibration frequency is also within the range of frequencies (4.5–60 Hz) reported in other animal studies.[8,10] Although the behavioral results of our study reflect outcomes only for a single vibration amplitude and frequency, that vibration profile is sufficient to produce behavioral sensitivity. In addition, the accelerometer was not mounted to the spine and so measurements do not reflect those of the spinal response alone. However, pilot studies (unpublished) indicate these responses to be similar for 15 Hz, especially under conditions with passive muscle contributions. Additional studies at different frequencies and amplitudes will help characterize injury resulting from WBV.

The sustained sensitivity that is produced in both the forepaw and hind paw by the *repeated WBV* exposure (Fig. 4) suggests that such exposure for even seven days is sufficient to induce chronic injury or a sustained modification in the nociceptive cascades. In contrast, although a single exposure induces behavioral sensitivity, it is short-lived and lasts only for 4 or 5 days in the forepaw and hind paw, respectively (Fig. 4). Interestingly, even though this resolves by Day 6 in the *intermittent WBV* group and returns to baseline levels, it is immediately re-established after the second exposure, but takes longer to resolve and exhibits a slower rate of recovery after a second exposure (Fig. 4). This heightened, longer-lasting behavioral sensitivity after a rest period and re-exposure suggests that the initial exposure may reduce the pain threshold or modulate the central mechanisms that contribute to pain so that the subsequent second exposure produces a more "severe" response than does the same exposure initially. This longer-duration of sensitivity after a re-exposure is consistent with the behavioral sensitivity response in a study in which the L5 lumbar nerve root was ligated and re-injured again 6 weeks later.[15] In that study, the behavioral response after the second injury was significantly increased over the response after the first injury.[15] However, no such similar increase in behavioral sensitivity was observed in the current study (Fig. 4), which may be due to the fact that a WBV induces a less-robust tissue injury. However, it is also possible that since the initial WBV reduces the response threshold to approximately 4 g-force (Fig. 4), this testing technique may not enable detection of an additional decrease in response threshold since there are only three other filaments (0.6, 1.4, and 2.0 g-force), with lower strengths, providing limited resolution to detect any changes between the first and second exposures. Nonetheless, additional studies using other measures of behavioral assessment may help characterize the extent and type of pain and functional deficits that may result from WBV.

The production of behavioral sensitivity after WBV is consistent with other models of pain from mechanical tissue loading.[13,15–17] A single transient mechanical loading to isolated nerve roots and facet joints in the cervical spine induces an immediate and sustained decrease in the response threshold.[13,17] Similarly, separate injuries to the lumbar nerve root or sciatic nerve also induce a sustained increase in behavioral sensitivity.[15,16] The behavioral data from those studies help to contextualize the extent and severity of tissue injury throughout the spine that may be responsible for pain after a WBV exposure. The *repeated WBV* induces sensitivity in both paws up to Day 14 (Fig. 4), but the behavioral assessments were performed for only 14 days, so long-term outcomes in these models still remain undetermined.

Although vibration exposure was imposed to the whole body (Fig. 2), there were differences detected between the withdrawal threshold of the forepaw and hind paw and between the deformation responses of the cervical and lumbar regions (Figs. 3 and 4). Both paws exhibited an overall difference in response threshold compared to *sham* for the *repeated WBV* group, but only the forepaw response was different from *sham* for the *intermittent WBV* group (Fig. 4). Also, the threshold for forepaw withdrawal was significantly lower in the *repeated WBV* group compared to *sham* on all days except Day 4, whereas it was only different on Days 8, 10, 12, and 14 compared to *sham* in the hind paw (Fig. 4). These differences in behavioral sensitivity may be due to the differences in compression and extension in the cervical and lumbar region during vibration. It is possible that the reduced paw withdrawal thresholds may be due to local effects of their direct loading. Yet, this is unlikely since such mechanical contributions were small; additional studies assaying tissues for markers of local injury will provide additional insight about whether WBV induces local, central, or combined effects leading to pain. Both compression and extension were induced in the lumbar and cervical spines (Fig. 3), with the extent of compression being significant in both, while extension was only increased in the cervical region. The extent of compression in the cervical region was nearly

double that in the lumbar region and cervical extension was 1.5 times greater than lumbar extension, which may be responsible for the more robust sensitivity in forepaw (Figs. 3 and 4).

This study suggests that a repeated WBV exposure for 30 min of 15 Hz vibration at a magnitude of 0.56 g establishes pain. Although vibration exposure was performed under inhalation anesthesia, which eliminates any contribution of the active musculature, this was still sufficient to induce behavioral sensitivity. Additional studies are needed to further define the role of active musculature in this and other similar models. Indeed, previous animal studies, also using anesthesia, have linked WBV to pain over a range of frequencies from 4.5 to 60 Hz.[8,10] Several neuropeptides related to nociception have been reported to change in the rabbit after a single 2 hr WBV exposure at 4.5 Hz with an amplitude of.0.35 g.[8] Substance P in the L4–L6 dorsal root ganglia decreased and vasoactive intestinal peptide increased as early as 30 min after a single WBV exposure, which is consistent with results seen in other painful peripheral nerve injuries.[8,18] In addition, arterial endothelial cell disruption has been reported to occur as early as 45 min after vibration of the tail at 60 Hz for 4 h in a rat.[10] Together, the molecular and cellular changes related to nociception and injury that have been reported in these other animal studies support the link between WBV exposure and pain, even for varying frequencies and amplitudes of exposures. Although the current study did not explicitly investigate the relationship between behavioral sensitivity and relevant physiological cascades related to pain, the results do demonstrate increased behavioral sensitivity after two different WBV exposure paradigms and suggest such future investigations to be worthwhile.

This model of vibration injury serves as a tool to further investigate the relationship between WBV and pain. Although the current study supports the hypothesis that vibration leads to pain, it does not identify the source of such modifications. Continued studies under different vibration conditions and incorporating assays of tissue mechanics, as well as markers of injury, inflammation and nociception, will enable a more complete definition of the relationship(s) between pain and injury. In particular, studies assaying neuroinflammatory responses in muscle, disc, and other tissues, together with expanded behavioral assessments will provide added insight about this type of painful injury.

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