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## Effect of Spinal Manipulation Thrust Magnitude on Trunk Mechanical Thresholds of Lateral Thalamic Neurons

**William R. Reed, DC, PhD [Associate Professor],**

Palmer Center for Chiropractic Research

**Joel G. Pickar, DC, PhD [Professor Emeritus],**

Palmer Center for Chiropractic Research

**Randall S. Sozio, BS,LATG [Research Associate], and**

Palmer Center for Chiropractic Research

**Cynthia R. Long, PhD [Professor, Director of Palmer Center of Chiropractic Research]**

Palmer Center for Chiropractic Research

### Abstract

**Objectives**—High velocity low amplitude spinal manipulation (HVLA-SM), as performed by manual therapists (eg, doctors of chiropractic and osteopathy) results in mechanical hypoalgesia in clinical settings. This hypoalgesic effect has previously been attributed to alterations in peripheral and/or central pain processing. The objective of this study was to determine whether thrust magnitude of a simulated HVLA-SM alters mechanical trunk response thresholds in wide dynamic range (WDR) and/or nociceptive specific (NS) lateral thalamic neurons.

**Methods**—Extracellular recordings were carried out in the thalamus of 15 anesthetized Wistar rats. Lateral thalamic neurons having receptive fields which included the lumbar dorsal-lateral trunk were characterized as either WDR (n=22) or NS (n=25). Response thresholds to electronic von Frey (rigid tip) mechanical trunk stimuli were determined in three directions (dorsal-ventral, 45°caudalward, and 45°cranialward) prior to and immediately following the dorsal-ventral delivery of a 100ms HVLA-SM at three thrust magnitudes (control, 55%, 85% body weight; (BW)).

**Results**—There was a significant difference in mechanical threshold between 85% BW manipulation and control thrust magnitudes in the dorsal-ventral direction in NS neurons ( $p=.01$ ). No changes were found in WDR neurons at either HVLA-SM thrust magnitude.

**Conclusions**—This study is the first to investigate the effect of HVLA-SM thrust magnitude on WDR and NS lateral thalamic mechanical response threshold. Our data suggest that at the single

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William R. Reed DC, PhD, william.reed@palmer.edu, 741 Brady Street, Davenport, IA 52803, 563-884-5145, 563-884-5227.

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lateral thalamic neuron level, there may be a minimal spinal manipulative thrust magnitude required to elicit an increase in trunk mechanical response thresholds.

## Keywords

spinal manipulation; thalamus; nociceptive neurons; lumbar vertebrae; chiropractic

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## Introduction

Spinal manipulation and spinal mobilization are commonly used in clinical practice to alleviate low back pain.<sup>1-3</sup> Although the underlying mechanisms remain unknown, these forms of manual therapy have been clinically shown to increase mechanical pressure pain thresholds (i.e. decrease sensitivity) in both symptomatic and asymptomatic subjects.<sup>4-12</sup> Cervical spinal manipulation has been shown to result in unilateral as well as bilateral mechanical hypoalgesia.<sup>6,7,12,13</sup> Compared to no manual therapy, oscillatory spinal manual therapy at T12 and L4 produced significantly higher paraspinal pain thresholds at T6, L1 and L3 in individuals with rheumatoid arthritis.<sup>4</sup> The immediate and widespread hypoalgesia associated with manual therapy treatments has been attributed to alterations in peripheral and/or central pain processing including activation of descending pain inhibitory systems.<sup>7,14-16</sup>

Increasing evidence from animal models suggests that manual therapy activates the central nervous system and in so doing affects areas well beyond those being treated.<sup>14,17,18</sup> Sluka and Wright<sup>19</sup> reported in rats that unilateral knee joint mobilization evokes bilateral hypoalgesia, suggesting a widespread centrally-mediated response to joint mobilization. More recently, it was shown that Grade 2 equivalent spinal mobilizations applied manually to the L5 spinous process increases hindpaw mechanical nociceptive thresholds in the awake rat with or without acute inflammation.<sup>17</sup> In addition, Song et al.<sup>20</sup> reported that instrument delivered HVLA-SM significantly reduces the severity and shortens the duration of pain and hyperalgesia caused by neural inflammation within the intervertebral foramen. These findings from animal models are consistent with the widespread hypoalgesic effects reported clinically following a manual therapeutic intervention. To what extent these hypoalgesic effects are attributable to central mechanisms is undetermined but alterations in convergent supraspinal nociceptive processing likely play a role.

The thalamus is subcortical structure receiving convergent input from all innocuous (dorsal column pathway) and/or nociceptive (spinothalamic pathway) somatosensory receptors stimulated during delivery of a spinal manipulation. The ability of the thalamus to modulate ascending sensory input as well as interact functionally with descending pain modulating structures such as the periaqueductal gray (PAG) is not well understood despite studies showing the existence of direct projections between multiple thalamic nuclei and the PAG.<sup>21-23</sup> Recently in humans it was demonstrated that the lateral thalamus and PAG interact reciprocally at short latencies (~5ms) and that stimulation of either structure relieved pain to various degrees.<sup>24</sup> Although more work in this area is required, the authors suggested that the thalamus and PAG influence each other in opposite ways via a fairly direct pathway not involving spinal cord circuitry and thereby being important in pain

perception.<sup>24</sup> Whether or not such a pathway could contribute to the immediate and widespread hypoalgesia following HVLA-SM is plausible but at this point purely speculative.

Optimization of the biomechanical features that characterize a spinal manipulation such as thrust magnitude, thrust duration, loading direction relative to the patient, tissue pre-load, and anatomical contact site, is thought to be critical to clinical expertise.<sup>25-28</sup> A pilot study investigating the relationship between the magnitude of the force applied and hypoalgesia in individuals with lateral epicondylalgia suggested that the amount of applied manual force may determine the extent of hypoalgesia.<sup>29</sup> The purpose of the present study was to determine the relationship between HVLA-SM thrust magnitude and trunk mechanical response threshold of lateral thalamic neurons in an animal model. Determination of which (if any) biomechanical characteristics of an HVLA-SM alter neural response characteristics has been the subject of several recent basic investigations.<sup>30-34</sup> Together, these studies aim to provide insight into the mechanisms underlying spinal manipulation.

## Methods

All experimental procedures were approved by the Institutional Animal Care and Use Committee. Animals were housed individually and exposed to a 12-h light/dark cycle with food and water ad libitum. For terminal electrophysiological recordings, all animals were anesthetized with an intraperitoneal (ip) injection of 50% urethane (1.2g/kg) and maintained with supplements (5% urethane) administered intravenously (iv) as needed.<sup>35,36</sup> Depth of anaesthesia was assessed by monitoring pinch withdrawal, corneal reflex, respiration rate and vibrissae movements to maintain an anaesthetic state III-3.<sup>35,37</sup> The jugular vein was catheterized and trachea intubated for the purposes of iv infusion and pCO<sub>2</sub> monitoring respectively. In addition, oxygen concentration, blood pressure, heart rate, and respiration were monitored by a Mouse Ox system (Starr Life Sciences Corp., Oakmont, PA). Body temperature was monitored with a rectal thermistor and maintained at 37°C with a circulating-water heating pad. The rat's head was secured with the dorsal surface positioned horizontally in a stereotaxic device (Kopf Instruments, Tujunga, CA). A small hole was made in the skull and expanded with bone rongeurs. The exposed dura mater was opened and the extracellular recording electrode was advanced into the thalamus.

## Electrophysiology

Single thalamic neurons were recorded extracellularly with DiI (1,1'-dioctadecyl-3,3,3',3'-tetramethyl-indocarbocyanine perchlorate; Invitrogen, Carlsbad, CA)-coated tungsten microelectrodes [6 to 8 M $\Omega$  impedance (FHC, Bowdoin, ME)] as previously described<sup>35,38,39</sup> (Fig. 1A). Thalamic tracks began 4mm below the surface of the cortex and ended at 7.5mm.<sup>40</sup> The tungsten electrode was slowly advanced at a rate of 1-5  $\mu$ m per step using a motorized micromanipulator (Neurostar, Germany) until spontaneous single unit activity was encountered. If the neuron's receptive field included the dorsal-lateral trunk then spontaneous activity was recorded for at least one minute prior to commencement of mechanical testing using the electronic von Frey anesthesiometer. Thalamic electrode tracks were made in parallel columns, 500 $\mu$ m apart, and were located between -2.04mm and

-3.30mm caudal to bregma and 1.2mm and 3.8mm lateral to midline.<sup>40</sup> Lateral thalamic subnuclei through which the electrode passed included: ventral lateral (VL), ventroposterolateral (VPL), posterior (Po), laterodorsal ventrolateral (LDVL), and laterodorsal dorsal medial (LDDM) (Fig. 1B). Thalamic neuron activity was passed through a high impedance probe (HIP511, Grass, West Warwick, RI) and then amplified (P511K, Grass) and recorded using a PC based data acquisition system (Spike 2, Cambridge Electronic Design, UK).

The neurons in this study were classified as either wide dynamic range (WDR) responding in a graded fashion to low threshold mechanical (brush stroke) and high mechanical (noxious pinch) or as nociceptive specific (NS) responding only to noxious pinch. Neurons responding solely to low threshold mechanical (brush stroke) trunk stimulation were not considered in this study.

Following recording of baseline thalamic neuronal activity, an electronic von Frey anesthesiometer with a rigid tip adapter (0.79mm<sup>2</sup> contact area; IITC Model 2390 [www.iitcinc.com](http://www.iitcinc.com)) was applied within the receptive field close to the midline of the dorsal trunk (within 2cm of the spine) in three directions: dorsal-ventral, 45°caudalward and 45°cranialward. It was thought that the direction with which the trunk stimuli were applied might differentially affect force transmission to the trunk peripheral mechanoreceptors and thereby impact thalamic response thresholds. The electronic vonFrey stimulus was manually applied in increasing magnitude until either a thalamic response was elicited or 400g had been applied to the trunk. If spontaneous bursting activity was present, mechanical testing occurred during intermittent silent periods or during periods of minimal tonic firing. Thalamic responses to low and/or to high threshold mechanical stimuli were recorded both prior to and following the delivery of a simulated high velocity low amplitude spinal manipulation (HVLA-SM). The directions in which electronic von Frey mechanical stimulus was applied were randomized before HVLA-SM to minimize possible ordering effects. Trunk testing locations were varied between different neurons to reduce potential long-term effects on thalamic neuronal activity such as sensitization or habituation.

### Spinal Manipulation

HVLA-SMs were delivered in the dorsal-ventral direction to the L5 vertebra. The lumbar spine was mechanically secured by clamping the L2 spinous process and fixing the iliac crests with hip pins (David Kopf Instruments, Tujunga, CA). A very small skin incision was made over the L5 vertebra through which a pair of adjustable toothed forceps was inserted and rigidly attached to the lateral surfaces of the L5 spinous process. In clinical settings, the HVLA-SM force-time loading profile can be likened to a triangle wave<sup>41,42</sup> with a thrust phase rising to a peak load in less than 150ms.<sup>41-43</sup> Clinically, manipulative thrust forces range from 31% to 78% body weight (BW) assuming an average human body weight of 70kg.<sup>44,45</sup> Therefore, HVLA-SMs were delivered as a triangle wave with a thrust phase of 100 ms and amplitudes of 55% BW or 85% BW (Fig. 1C). Prior to the delivery of each manipulative thrust, the lumbar spine was positioned neutrally with neither force nor displacement being applied by the motor to the L5 vertebra. The testing order of the three thrust magnitudes [control (i.e. 0% BW), 55% BW, 85% BW] was randomized for each

neuron within each direction yielding a randomized complete block design. A period of five minutes lapsed between manipulations which appears to be adequate time to mitigate viscoelastic tissue changes related to HVLA-SM.<sup>46</sup>

## Histology

Following extracellular thalamic recordings, the rat was perfused transcardially with 0.9% saline followed by 4% paraformaldehyde. The brain was removed and stored in a 30% sucrose/10% formalin solution at 4°C until sectioning. Brains were cut with a cryostat (30µm sections) and mounted on microscope slides. Electrode track locations confirmed (Fig. 1A) with postmortem histological reconstructions using with a Nikon Optiphot microscope with EFD-EPI fluorescent attachment and illumination system with adjacent sections stained with cresyl violet as previously established.<sup>35,38,39,47-49</sup>

## Data Analysis

Data analyses were conducted using SAS (version 9.2, SAS Institute, Cary, NC). For each mechanical testing direction, by neuron classification, a one-way analysis of variance (ANOVA) for a randomized complete block design, with neuron as the block, was used to test between thrust magnitudes. Statistical significance was set at .05. Mean changes between pre- and post HVLA-SM mechanical thresholds and 95% confidence intervals under the ANOVA model are given in figures; mean differences between both control and 55% BW with 85% BW and 95% confidence intervals (lower, upper) from the ANOVA model are given in the text.

## Results

Electrophysiological activity of 47 thalamic neurons located in lateral thalamic subnuclei which responded to mechanical stimulation applied to the lumbar dorsal-lateral trunk were obtained from 15 adult male Wistar rats (330-540g) (Fig. 2). Of these neurons, 47% (22/47) were classified as WDR neurons and 53% (25/47) were classified as NS neurons. The mean rate of spontaneous activity was 4.64 imp/s (SD 2.58) for WDR neurons and 3.76 imp/s (SD 2.51) for NS neurons. An example of a WDR neuron's response to 45° cranialward and dorsal-ventral mechanical trunk stimulation prior to HVLA-SM is shown in Fig. 3.

Changes in WDR mean trunk mechanical threshold evoked by HVLA-SM were not significantly different among the three thrust magnitudes (control-0%, 55%, 85% BW) during dorsal-ventral testing ( $F_{2,42}=0.32$ ,  $p=0.73$ ; Fig. 4A), 45° caudalward ( $F_{2,42}=0.34$ ,  $p=0.71$ ; Fig. 4B) nor the 45° cranialward ( $F_{2,42}=0.85$ ,  $p=0.44$ ; Fig. 4C) testing directions.

Changes in NS neuron mean trunk mechanical threshold evoked by HVLA-SM were significantly different among the three HVLA-SM thrust magnitudes during dorsal-ventral testing ( $F_{2,48}=3.45$ ,  $p=0.04$ ; Fig. 4A), but not during the 45° caudalward ( $F_{2,48}=1.88$ ,  $p=0.16$ ; Fig. 4B) or 45° cranialward ( $F_{2,48}=0.74$ ,  $p=0.48$ ; Fig. 4C) testing directions. During dorsal-ventral testing, the 85% BW mean HVLA-SM thrust magnitude was significantly different from control (53.0g,  $p=.01$ , 95% CI: 12.3, 93.6) but not the 55% BW mean HVLA-SM thrust magnitude (30.2g,  $p=0.14$ , 95% CI: -10.5, 70.8).

Four WDR neurons that responded to brush stroke prior to the HVLA-SM ceased to respond to this innocuous type of mechanical stimulation following the higher (85% BW) but not lower (55% BW) manipulative thrust magnitude. The remaining 18 WDR neurons which also responded to brush stroke were unaffected by HVLA-SM.

## Discussion

In rats, axons from as many as 6000 spinal neurons project to the thalamus.<sup>50</sup> Both innocuous and noxious sensory inputs from A $\beta$ , A $\delta$ , and C fibers in cutaneous nerves and group II, III, and IV fibers in muscle nerves converge in the thalamus.<sup>51-53</sup> For example, wide dynamic range thalamic cells located in the lateral VPL-VL subnuclei respond to noxious stimulation of muscle and tendon while also responding to innocuous stimulation of the skin.<sup>54</sup> The lateral thalamic subnuclei, more specifically the ventral posterior nuclei (VPL, Po) are the primary terminus for spinothalamic inputs from both sides of the spinal cord.<sup>55</sup> However in the rat, one must be mindful that an estimated 15-20% of all spinothalamic tract neurons have branches terminating in both medial and lateral thalamic nuclei<sup>56,57</sup> indicating a much broader influence on different aspects of the pain matrix. With the thalamus's role of processing innocuous and noxious sensory input along with its diffuse network of connections, it is rational to think that convergent input and reciprocal feedback from pain matrix structures to the thalamus could play a part in the immediate and widespread hypoalgesic effects associated with manual therapy intervention. To our knowledge, this study is the first to investigate the effects of HVLA-SM thrust magnitude on the mechanical thresholds of thalamic neurons.

Relative to control, the 85% BW thrust magnitude HVLA-SM significantly increased mechanical thresholds of lateral thalamic NS neurons to dorsal-ventral mechanical testing of the trunk. Since the mechanical thresholds to 45°caudalward and 45°cranialward testing directions did not significantly differ relative to control, the decrease in trunk mechanical sensitivity likely was not a generalized response. In addition, the majority of WDR neurons (84%) retained their responsiveness to innocuous trunk stimulation following the 85% BW manipulative thrust magnitude suggesting no adverse effects to neural tissue.

The finding that only the higher intensity manipulative stimulus (i.e. 85% BW vs 55% BW or control) decreased the mechanical sensitivity of lateral thalamic neurons to mechanical trunk stimulation coincides with other reports relating graded mechanical or electrical stimulus intensity to the magnitude of central inhibition<sup>58,59</sup> but is in contrast to a recent clinical study reporting no differences in pressure pain thresholds in subjects receiving different amplitudes of posterior-anterior lumbar mobilizations.<sup>5</sup>

Several clinical studies indicate that spinal manipulation alters central processing of mechanical stimuli evidenced by increased pressure pain thresholds and decreased pain sensitivity in asymptomatic and symptomatic subjects following manipulation.<sup>6,7,11,60,61</sup> However, questions of mechanism and whether certain biomechanical dose characteristics of spinal manipulation and/or mobilization such as force magnitude, force duration, loading direction (relative to the patient), anatomical contact point, frequency and amplitude of oscillation are required for eliciting hypoalgesia are just beginning to be

investigated.<sup>5,10,30,32</sup> Krouwel et al.<sup>5</sup> recently reported no significant difference in hypoalgesia among subjects receiving different amplitudes of lumbar posterior-anterior mobilizations while Pentelka et al.<sup>10</sup> reported that at least four sets of large amplitude lumbar mobilizations (instead of the three sets used traditionally) were required to elicit hypoalgesia. Moss et al.<sup>9</sup> suggested that the repetitiveness of movement should be considered as the hypoalgesic stimulus rather than the pressure being used during joint mobilization procedures and this concept appears to be supported by the recent findings of Pentelka et al.<sup>10</sup> It may be found that a threshold force is required to elicit hypoalgesic effects during short duration manual procedures such as HVLA-SM but is unnecessary when using slower repetitive interventions such as spinal mobilization.

### Limitations

Spinal cord tissue was not harvested nor evaluated histologically. The possibility that an 85% BW thrust magnitude HVLA-SM may have resulted in trauma to underlying neural tissue and thereby influence the outcome is highly unlikely since significant threshold changes were not seen in all mechanical stimuli testing directions following the higher magnitude thrust. This conclusion is further supported by the finding that the 85% BW manipulative thrust failed to eliminate the responsiveness to innocuous trunk stimulation in the vast majority of thalamic neurons. In addition, similar HVLA-SM procedures with thrust magnitudes of 85% - 100% BW have been applied in other animal studies without any indication of neural trauma or underlying tissue damage<sup>31,62</sup> and similar forces are applied safely in clinical settings.<sup>41-43</sup>

Our use of a single application of the electronic von Frey mechanical stimulus to the trunk in a given direction prior to and following a spinal manipulation rather than performing multiple applications (3-10x) as with classical von Frey<sup>63</sup> or electronic von Frey<sup>64,65</sup> studies may have contributed to the variability we observed in thalamic responses (Fig. 4). The decision to use a single electronic von Frey application to the trunk in any given direction was made to limit potential sensitization and/or tissue damage which can occur from repetitive mechanical stimulations. Mechanically testing in three directions (dorsal-ventral, 45°caudalward, 45°cranialward) prior to and following three thrust magnitudes of (0%-control, 55% BW, 85% BW) equated to 9 mechanical stimulations per neuron. Applying multiple von Frey stimulations per direction would have greatly increased this number of applied mechanical stimulations which may have resulted in sensitization and/or tissue damage. Despite having used single trunk applications of the electronic von Frey in the past,<sup>35</sup> future studies should consider decreasing the number of mechanical stimulus directions tested while increasing the number of electronic von Frey applications in a given direction to reduce variability while limiting the potential sensitization or tissue damage.

Trunk mechanical stimuli responses were recorded in multiple lateral thalamic nuclei. Although there is collateral branching of projection fibers among thalamic nuclei along with degrees of functional overlap, it is recognized that several lateral thalamic nuclei included within this study make distinct contributions to somatosensory and/or nociceptive processing. Future studies may wish to concentrate on recording from single thalamic nuclei (i.e. VPL, Po, VL) or those nuclei which are closely related functionally.

It should be noted that whether or not changes in thalamic mechanical response thresholds are related to the clinically reported hypoalgesia following spinal manipulation remains to be determined. It is widely recognized that clinical pain, nociception and pain relief are multifactorial and complex in nature involving multiple spinal and supraspinal centers. Whether HVLA-SM's specific thrust magnitude or any other biomechanical dosage characteristics are required to produce antinociceptive or hypoalgesic related responses in other ascending or descending supraspinal pain processing centers such as the medullary reticular formation or periaqueductal gray remains to be determined.

## Conclusion

To our knowledge, this study is the first to investigate the effects of spinal manipulation and its thrust magnitude on the response properties of supraspinal neurons. The results suggest that at the level of a single lateral thalamic neuron, there may be a minimal thrust magnitude required for spinal manipulation to elicit an increase in the response thresholds of NS thalamic neurons to mechanical stimulation of the trunk. Larger studies examining the effects of thrust magnitude and other clinician-controlled mechanical HVLA-SM parameters on thalamic, brainstem, and cortical neurons known to be involved in nociceptive somatosensory processing need to be performed to confirm and extend the present findings and help elucidate the underlying mechanisms of spinal manipulation induced hypoalgesia.

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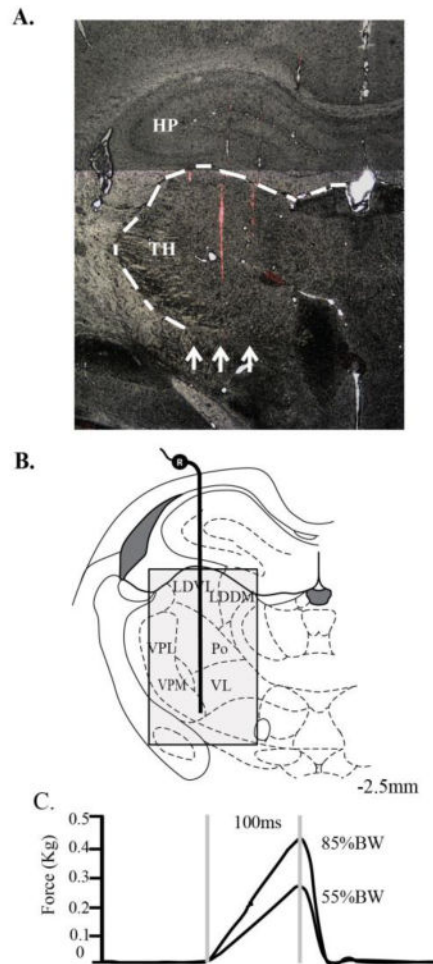
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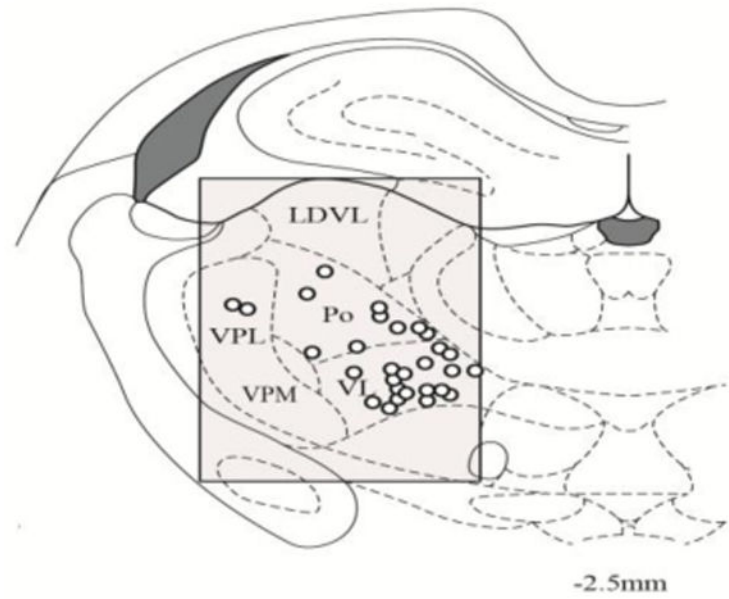
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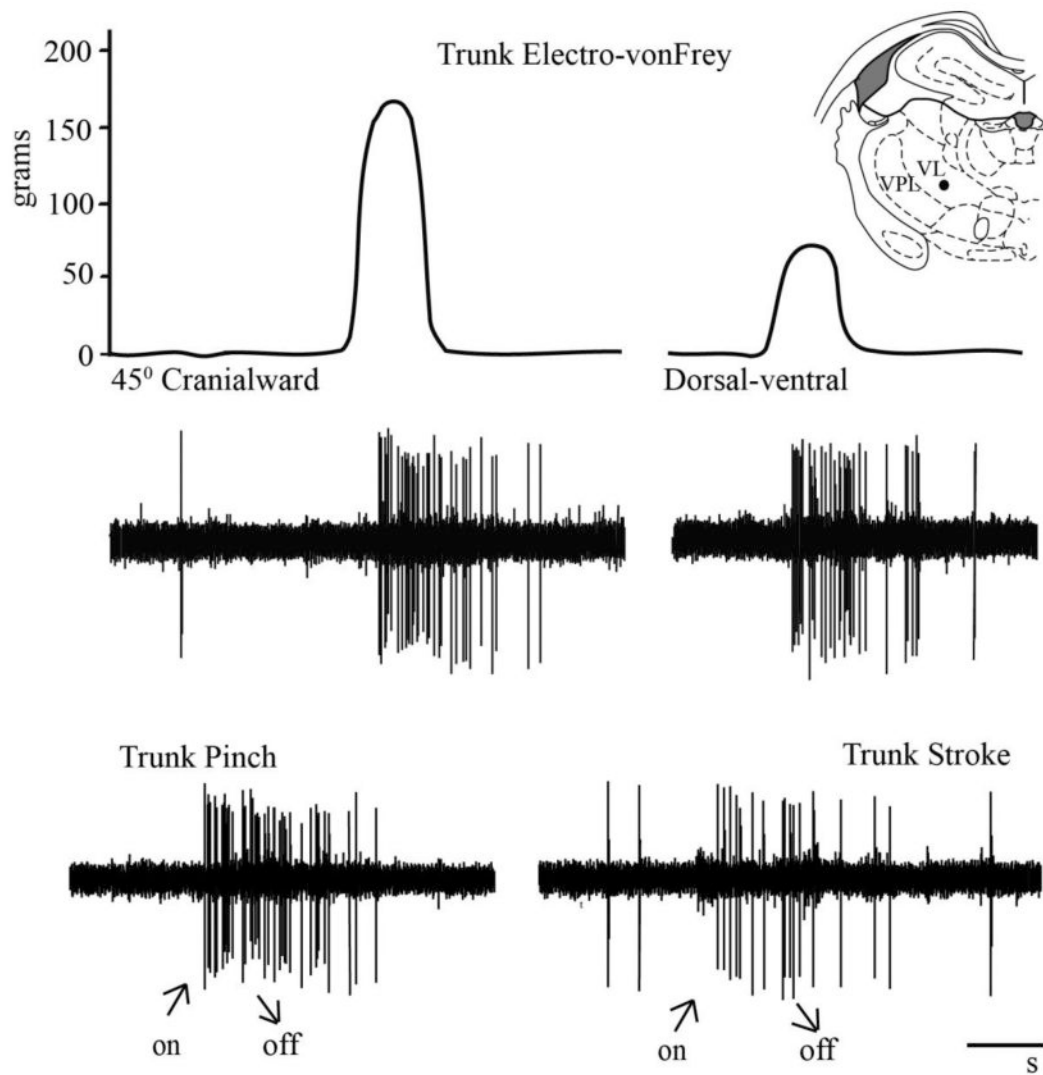


**Fig. 1.**

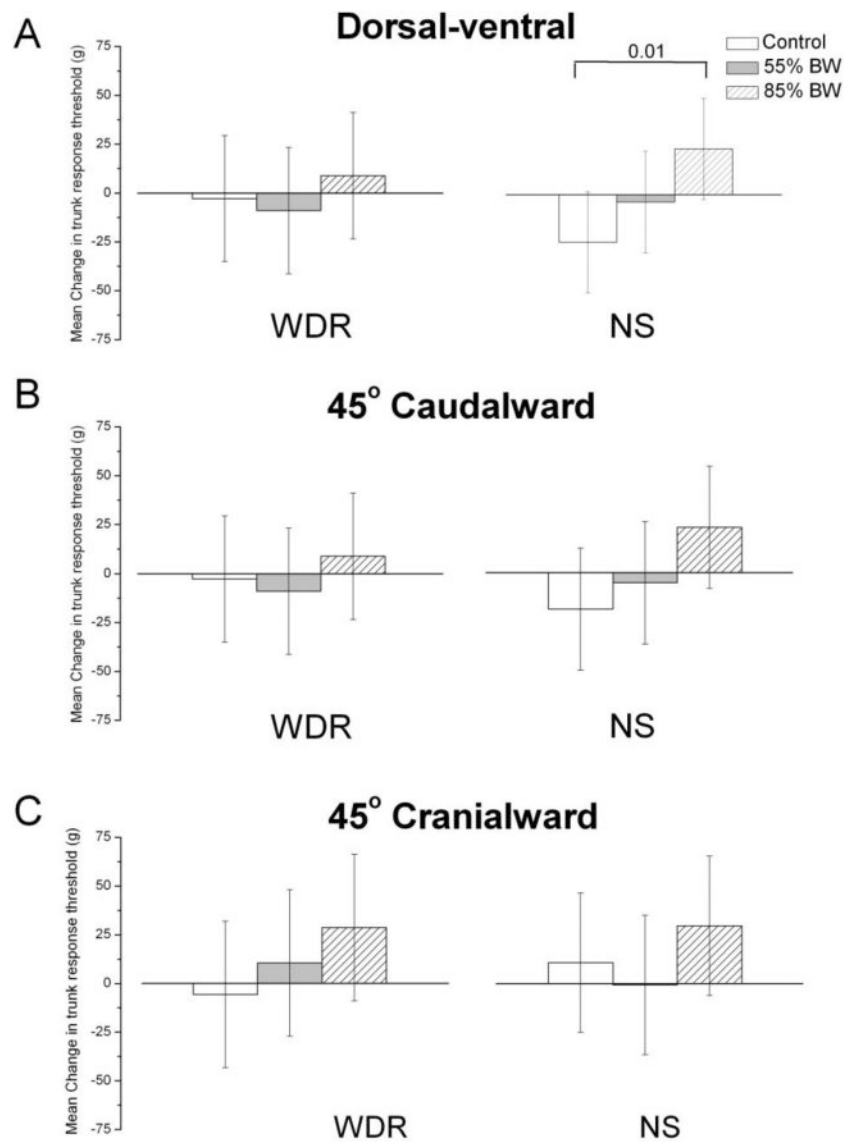
(A). Example of tracks (arrows) from Dil-coated electrodes through the lateral thalamus (TH) and hippocampus (HP) in a coronal brain section at 40x magnification. Of the three Dil electrode tracks shown, the medial & lateral Dil tracks are seen in greater detail in adjacent tissue sections; (B). A diagram illustrating the experimental setup for extracellular thalamic recordings at -2.5mm caudal to bregma. Shading indicates search area which included the laterodorsal dorsal medial (LDDM), laterodorsal ventrolateral (LDVL), ventrolateral (VL), posterior (Po), ventroposteromedial (VPM), and ventroposterolateral (VPL) nuclei; (C). Force profiles for L<sub>5</sub> spinal manipulative thrust with 100ms duration at 55% and 85% bodyweight.



**Fig. 2.** Summary showing the location (open circles) of 29/47 lateral thalamic neurons responding to mechanical stimulation applied to the trunk at -2.5mm caudal from bregma level. The shading indicates the search area. The remaining 18 neurons not shown were located at different thalamic levels.



**Fig. 3.** Trunk mechanical stimuli (upper row) responses of a single wide dynamic range thalamic neuron located (●) in the ventral lateral (VL) nucleus at -2.5mm caudal to bregma. Raw electrophysiological recordings (lower rows) of responses to lumbar trunk electronic von Frey stimuli in the 45° cranialward (161g) and dorsal-ventral direction (69g). Note graded response to trunk stroke and trunk pinch. Cal bar = 1s.



**Fig. 4.** Mean HVLA-SM changes in lumbar trunk electronic von Frey mechanical activation response thresholds (grams) for the dorsal-ventral, 45° caudal and 45° cranial directions of wide dynamic range (WDR) and nociceptive specific (NS) lateral thalamic neurons following time-control, 55% and 85% body weight high velocity low amplitude spinal manipulation thrust duration. Data are reported as means and 95% confidence intervals (lower, upper 95% CI).