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RESEARCH ARTICLE

# Decreased spontaneous activity and altered evoked nociceptive response of rat thalamic submedius neurons to lumbar vertebra thrust

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**Abstract** The thalamus is a central structure important to modulating and processing all mechanoreceptor input destined for the cortex. A large number of diverse mechanoreceptor endings are stimulated when a high velocity low amplitude thrust is delivered to the lumbar spine during spinal manipulation. The objective of this study was to determine if a lumbar thrust alters spontaneous and/or evoked nociceptive activity in medial thalamic submedius (Sm) neurons. Extracellular recordings were obtained from 94 thalamic Sm neurons in 54 urethane-anesthetized adult Wistar rats. Spontaneous activity was recorded 5 min before and after an $L_5$ control (no thrust) and thrust (85% rat body weight; 100 ms) procedure. In a subset of responsive nociceptive-specific neurons, mean changes in noxious-evoked response (10-s pinch with clip; 795 g) at three sites (tail, contra- and ipsilateral hindpaw) were determined following an $L_5$ thrust. Mean changes in Sm spontaneous activity (60 s bins) and evoked noxious response were compared using a mixed model repeated measures ANOVA with Bonferroni post hoc *t* tests and paired *t* tests, respectively. Compared to control, spontaneous Sm activity decreased 180–240 s following the lumbar thrust ($p < 0.005$). Inhibitory evoked responses were attenuated in the contralateral hindpaw following an $L_5$ thrust compared to control ($p < 0.05$). No other changes in spontaneous or noxious-evoked Sm activity were found. A delayed, but prolonged suppression of spontaneous Sm activity along with changes in noxious-evoked inhibitory responses in the contralateral hindpaw following lumbar vertebra thrust suggest that thalamic submedius neurons may play a role in central pain modulation related to manual therapy intervention.

**Keywords** Thalamus · Submedius · Neurophysiology · Spinal manipulation · Lumbar spine · Pain

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## Introduction

The thalamus is a central structure consisting of a large collection of individual subnuclei that process and modulate all mechanoreceptor/nociceptor input destined for the cortex (Jones 2007; Yen and Lu 2013). The thalamic submedius (Sm) nucleus is medially located and is frequently divided into rostral and caudal parts (Craig and Burton 1981; Dado and Giesler 1990; Yoshida et al. 1991, 1992). The Sm receives afferent projections from the lateral hypothalamus, orbital cortex, trigeminal sensory nucleus, medial parabrachial nucleus, raphe nuclei, and bilateral dorsal horn neurons throughout the entire spinal cord. Spinal projections primarily terminate in the rostral half of Sm in both the cat and rat, while spinal trigeminal nuclei projections terminate in the caudal half (Craig and Burton 1981; Craig et al. 1982; Dado and Giesler 1990; Blomqvist et al. 1992; Yoshida et al. 1992). In the cat, spinal projections arise almost exclusively from the marginal zone (lamina I), whereas in the rat the trigeminal projections arise from lamina I while the vast majority of spinal projections

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arise from the deep dorsal horn and intermediate zone/ventral horn (lamina V–VII) (Dado and Giesler 1990; Yoshida et al. 1991, 1992). Electrical stimulation, lesions, and pharmacological microinjections of the Sm nucleus have been shown to modulate pain response in animals. (Roberts and Dong 1994; Zhang et al. 1995, 1998, 1999; Xiao et al. 2005; Feng et al. 2008; Wang et al. 2008; Erfanparast et al. 2015). Evidence indicates that the Sm nucleus is involved in opioid receptor-mediated nociception modulation (Wang et al. 2008; Tang et al. 2009; Erfanparast et al. 2015), and as part of this nociceptive modulatory pathway, Sm efferent fibers terminate most heavily in the ipsilateral ventrolateral orbital cortex (VLO), lateral orbital cortex, and to a lesser extent in the insular cortex (Craig and Burton 1981; Yoshida et al. 1992; Tang et al. 2009). In addition to reciprocal connections between the Sm and VLO, VLO neurons also project to the midbrain periaqueductal gray (PAG), (Hardy and Leichnetz 1981; Craig et al. 1982) a region extensively implicated in descending inhibition of nociceptive inputs at the spinal cord level. The submedius nucleus subserves a number of physiological functions, but afferent and efferent connections along with behavioral and electrophysiological studies support a direct involvement of the Sm in mechanical/thermal nociceptive modulation.

Spinal manipulation is a non-pharmacological integrative healthcare intervention that is recommended by clinical guidelines and evidence reports for treating certain types of neck and low back pain (Chou et al. 2007, 2017; Bronfort et al. 2010). However, its efficacy and appropriate utilization are hindered due to the lack of current knowledge regarding its underlying neurophysiological mechanisms. Lumbar spinal manipulation is a mechanical stimulus that typically involves applying a single, short lever, high velocity, low amplitude posterior–anterior thrust of short duration (≤150 ms) to a particular vertebra equating to 30–130% body weight of a 70 kg individual (Herzog et al. 1993; Triano 2001; Bergmann 2005; Herzog 2010). Similar biomechanical thrust characteristics have been simulated and scaled for use in various animal models (Pickar 1999; Reed et al. 2013, 2014a). Clinically, mechanical and thermal pain thresholds are increased (i.e., decrease tissue sensitivity) within 5 min of the manipulative thrust in areas local and remote to those being treated in both symptomatic and asymptomatic individuals (George et al. 2006; Bialosky et al. 2009b, 2014; Coronado et al. 2012). This widespread hypoalgesia has been attributed to alterations in central pain processing (Wright 1995; Boal and Gillette 2004; Bialosky et al. 2009a), but the central pathways, structures, and mechanisms responsible remain undefined and thereby provides the underlying scientific rationale for the current study.

In the rat, submedius neurons typically have large (often bilateral) receptive fields and respond predominately to noxious convergent sensory input from spatially separated cutaneous, muscle, joint, and visceral tissues which suggests a non-discriminatory role in nociception (Miletic and Coffield 1989; Dostrovsky and Guilbaud 1990; Fu et al. 2002). These attributes are particularly relevant to manual therapy because spinal manipulation has been hypothesized to stimulate as many as 40 types of peripheral receptors in both cutaneous and deep spinal tissues (Gillette 1987). Taken together, these neuronal characteristics make Sm nociceptive-specific neurons good candidates for investigating supraspinal neurophysiological changes related to lumbar vertebra thrusts. The purpose of this study was to determine if adult rat lumbar vertebrae high velocity low amplitude thrusts alter spontaneous and/or evoked noxious thalamic Sm activity.

## Materials and methods

All experimental methods were approved by the Institutional Animal Care and Use Committee. Animals were housed in pairs and exposed to a 12-h light/dark cycle, environmental enrichment with food and water ad libitum. For electrophysiological recordings, 54 adult male Wistar rats (320–524 g; Envigo, Indianapolis, IN, USA) were initially anesthetized with isoflurane (2.5%) followed by an intraperitoneal injection of 50% urethane (1.2 g/kg). The jugular vein and carotid artery was catheterized for intravenous (iv) infusion of fluids and blood pressure monitoring. The trachea was intubated for $pCO_2$ monitoring. Saturated oxygen concentration, heart rate, and respiration were monitored by a MouseOx system (Starr Life Sciences Corp., Oakmont, PA, USA). Body temperature was monitored via a rectal thermometer and maintained at 37 °C with a water-circulating heat pad. To maintain an anesthetic state III-3 (Friedberg et al. 1999) throughout the duration of the experiment, depth of anesthesia was regularly assessed by monitoring hindpaw pinch withdrawal, corneal reflex, heart rate, respiration rate and vibrissae movements. Supplemental anesthesia (5% urethane; iv) was administered as indicated (Hubscher and Johnson 2003; Reed et al. 2009).

### Electrophysiology

The rat's head was secured in a stereotaxic device (Kopf Instruments, Tujunga, CA, USA) with its dorsal surface positioned horizontally. A small hole was made bilaterally in the skull just lateral to midline and then expanded carefully with a small bone rongeurs to avoid rupture of the superior sagittal sinus. The dura was opened and the recording electrode was advanced incrementally into the thalamic submedius nucleus. Warm mineral oil was used to prevent tissue desiccation. Activity of thalamic Sm neurons

was recorded extracellularly with DiI-(1,1′-dioctabecyl-3,3,3′,3′-tetramethyl-indocarbocyanine perchlorate; Invitrogen, Carlsbad, CA, USA) coated tungsten microelectrodes (FHC, Bowdoin, ME, USA) having 6–8 MΩ impedance as previously described (Massey et al. 2006; Chadha and Hubscher 2008; Reed et al. 2009, 2014a). Thalamic submedius nuclei search coordinates were between −2.3 and −2.6 mm caudal to bregma, 0.5 and 0.9 mm lateral to midline, and 6.0–6.9 mm below the cortex surface (Fig. 1a) (Kawakita et al. 1993; Sumiya and Kawakita 1997; Yang and Follett 2003). The electrode was slowly advanced at a rate of 1–5 µm per step using a motorized micromanipulator (Neurostar, Germany) (Fig. 1b) until spontaneous isolated single unit Sm activity was identified. Signals from single thalamic Sm neurons were passed through a high impedance probe (HIP511, Grass, West Warwick, RI, USA), amplified (P511K, Grass), recorded and evaluated off-line using a PC based data acquisition system (Spike 2, Cambridge Electronic Design, UK). Neuron receptive fields were mapped and recorded. All Sm neurons included in this study were classified as nociceptive-specific (high threshold) neurons due to a lack of response to low threshold stimulation (innocuous stroking with nylon brush). While not exclusive, nociceptive-specific neurons are the predominate type of Sm neuron found in the normal rats (Dostrovsky and Guilbaud 1988; Miletic and Coffield 1989; Kawakita et al. 1993).

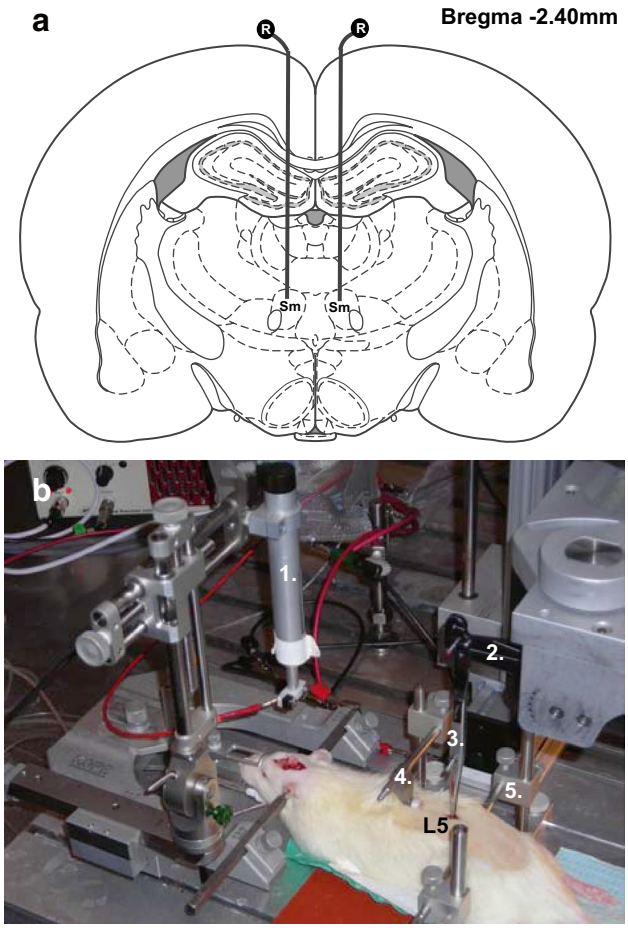


**Fig. 1** Experimental setup. Schematic showing the recording location of the thalamic submedius (Sm) neurons (**a**); and the experimental set-up (**b**) including the microdrive (*1*), lever arm of feedback motor (*2*), toothed forceps attached to the $L_5$ spinous process (*3*), and spinal stabilization clamp attached to the L2 spinous process (*4*), and hip pins (*5*)

### Spontaneous activity

The effect of high velocity low amplitude lumbar thrusts on spontaneous activity was determined as follows. Once single unit thalamic Sm activity was isolated, a timed-control protocol was performed. This consisted of recording spontaneous neural activity for 5 min before and after a no thrust procedure. Afterwards, spontaneous activity was again recorded for 5 min before and after a lumbar thrust protocol (peak amplitude of 85% rat body weight, 100 ms duration) (Reed et al. 2014a, b). Neural activity was quantified as impulses per period of time (10 or 60 s intervals). A computer controlled electronic feedback system (Lever System Model 310; Aurora Scientific, Ontario, Canada) (Pickar 1999) was used to deliver a linearly increasing dorsal–ventral thrust force at the $L_5$ vertebra via toothed forceps attached to the spinous process (Fig. 1b). Prominent rat boney landmarks (ridge of iliac crests and large $L_6$ spinous process) were used to identify the $L_5$ spinous process for forceps attachment. The scaled $L_5$ thrust profile simulates the thrust magnitude, thrust duration and vertebrae displacement (0.5–1.5 mm) of that delivered in clinical settings (Herzog et al. 1993; Nathan and Keller 1994; Gal et al. 1997; Triano 2001; Ianuzzi and Khalsa 2005) albeit via forceps attached directly to spinous process so as to directly determine the amount of vertebra displacement. For spontaneous activity recordings, the control (no thrust) protocol always preceded the lumbar thrust protocol so as to prevent any potential long-lasting influence related to the thrust.

### Noxious-evoked response

To determine the effects of high velocity low amplitude lumbar thrusts on evoked Sm noxious response, a 10 s noxious pinch stimulus (small clip; 795 g; Roboz-RS 5452, Gaithersburg, MD, USA) was applied in random order to three sites (tip of the tail, contra- and ipsilateral hindpaws) prior to and following control and thrust procedures. To minimize the risk of potential peripheral sensitization, responses to evoked noxious stimulation (at three sites) was performed on one Sm neuron

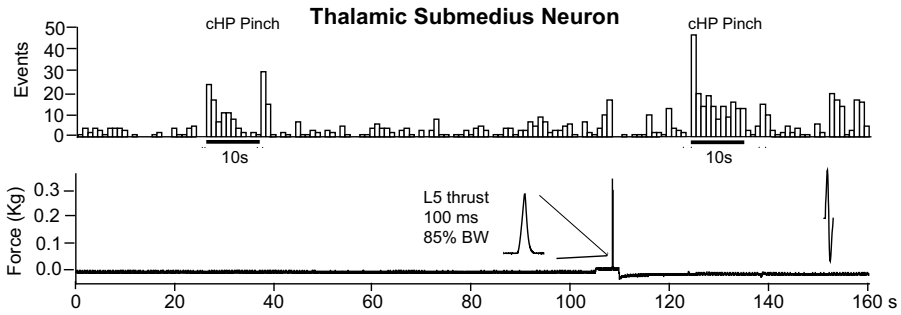


**Fig. 2** Thrust protocol example. Shows a histogram (*top*) of neural activity recorded from a submedius neuron during 10 s noxious stimulation (clip) applied to the contralateral hindpaw (cHP pinch). Pinches were applied approximately 60 s prior to and 10–15 s following an $L_5$ vertebra thrust [85% body weight (BW) 100 ms duration]. *Insets* show the waveform for the $L_5$ vertebra thrust and action potential of this thalamic neuron. Control protocols were the same only without the thrust

per hemisphere. An example of a thrust protocol neural recording is shown in Fig. 2. The order of control and thrust protocols for noxious-evoked Sm activity were randomized to minimize any possible ordering effects in addition to a waiting period of 5 min between test protocols. The 10-s duration of noxious pinch stimulus has been used in previous studies of thalamic neuron responsiveness (Zhao et al. 2006; Fischer et al. 2009). Spontaneous (resting) activity (10 s) immediately preceding each pinch stimulus was subtracted from the 10-s evoked responses to yield a net discharge for the noxious stimulus. Changes in evoked Sm response were determined by subtracting the net discharge of 1st pinch stimulus from the net discharge of the 2nd pinch stimulus.

## Histology

Following experimental protocol completion, electrolytic lesions were made by applying 30 µA current for 30 s. Afterwards, transcardiac perfusions were performed with an oxygenated calcium-free Tyrodes buffer solution followed by 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4 (Onifer et al. 2005). The brains were removed and post-fixed overnight at 4 °C, and then transferred to 30% sucrose at 4 °C for a minimum of 36 h prior to coronal tissue sectioning (30 µm) using a cryostat. DiI-labeled electrode tracks were located using a Nikon microscope equipped with fluorescent filters. Select sections were then stained with cresyl violet and postmortem histological reconstructions were performed using a combination of stereotaxic coordinates records, DiI-labeled electrode track measurements (Hubscher 2006; Massey et al. 2006; Reed et al. 2009) and electrolytic lesions (Fig. 3). Neurons identified as being outside the confines of the Sm nucleus were excluded.

## Statistical analysis

Changes in mean spontaneous responses (impulses/time bin) from control and $L_5$ thrust protocols were compared using a mixed model repeated measures ANOVA followed by Bonferroni post hoc *t* tests (IBM SPSS v22, Armonk, NY, USA). For spontaneous activity analyses, the 5 min

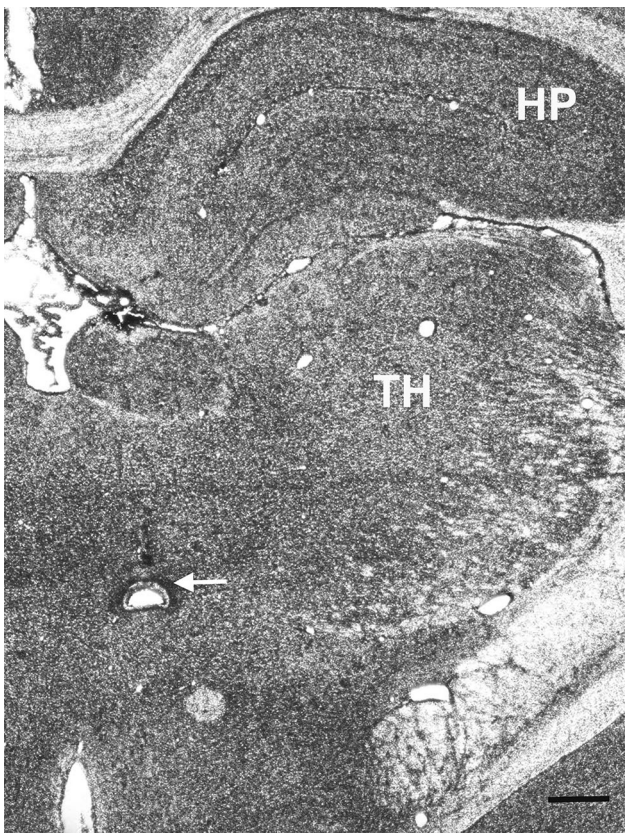


**Fig. 3** Electrolytic lesion site. Photomicrograph showing recording and electrolytic lesion site (*arrow*) with Di-I in the thalamic nucleus submedius (Sm). *HP* hippocampus, *TH* thalamus. *Scale bar* 0.5 mm

pre- and post-procedure recording periods were subdivided into five 60 s bins (60, 120, 180, 240, 300 s). To evaluate the possibility of a more immediate change in spontaneous activity due to lumbar thrust, changes in neural activity for the 10 s immediately following each procedure were also compared. Outlier values (≥ or ≤3 standard deviations from the mean) were removed to prevent the undue influence of atypical thalamic neural activity (prolonged bursting or silence) during the 10 min protocol recording period. Outlier removal resulted in spontaneous activity from 86 to 91 Sm neurons being compared per time interval. For evoked response analysis, 55/94 Sm neurons were tested (noxious testing was limited to one neuron per thalamic hemisphere). Only Sm neurons exhibiting greater than 20% increase over initial pre-pinch baseline activity (10 s) at individual test sites were considered to be responsive to noxious stimulation. These criteria ensured that the stimuli was applied within the neuron's receptive field and resulted in the analysis of 35–43 neurons at a given site for single factor paired *t* tests comparisons. Data shown are mean ± SEM unless otherwise noted and statistical significance was set at $p \leq 0.05$.

## Results

While the entire rostral–caudal extent of the submedius nucleus was searched, the majority (68%) of the 94 single unit recordings were located in the rostral half of the nucleus having a mean depth of 6.41 mm (±0.28 SD) from the cortical surface. All Sm neurons were classified as nociceptive specific (high threshold) by their lack of response to innocuous stroking (brush) and exhibited an excitatory response to noxious pinch (forceps). Lumbar thrust displacement–time profiles mirrored those of the "inverted V" shape of clinical force–time profiles (Herzog et al. 1993; Triano 2001) with a mean $L_5$ displacement of 1.02 mm (±0.47 mm SD).

### Spontaneous activity

All recorded Sm neurons were spontaneously active to some degree. Prior to peripheral stimulation, 22 (23%) neurons had a low firing rate (<1 Hz), 69 (73%) a moderate rate (1–10 Hz) and 3 (3%) a high firing rate (>10 Hz). Compared to the control procedure, there were no significant changes in mean Sm spontaneous activity during the first 180 s following the $L_5$ vertebra thrust. However, spontaneous Sm activity was significantly decreased 180–240 s after the thrust (ANOVA: $F = 4.8$, $df = 1.5$, $p < 0.05$, post hoc: $p < 0.005$) (Fig. 4; Table 1). Decreased spontaneous Sm activity continued into the subsequent 60 s bin (from 240 to 300 s) but failed to reach significance (Fig. 4).

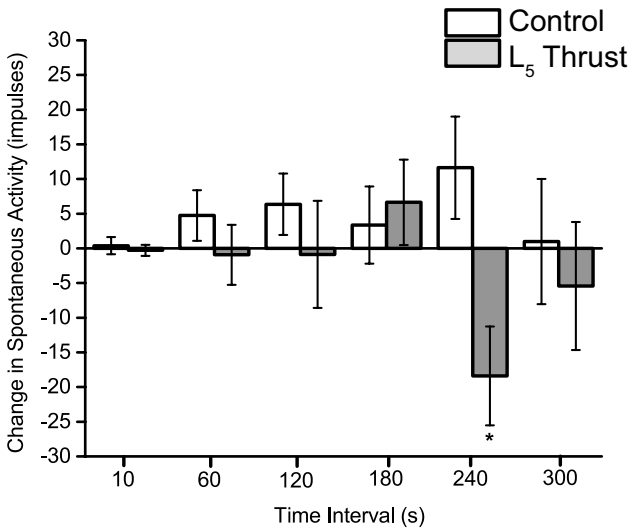


**Fig. 4** Spontaneous activity. Mean changes (±SEM) in spontaneous activity of nociceptive-specific submedius neurons before and after a control and high velocity low amplitude $L_5$ vertebra thrust procedures. Note a significant decrease of spontaneous activity 180–240 s after the delivery of the $L_5$ thrust (*$p < 0.005$)

**Table 1** Mean changes and SEM in spontaneous discharge activity (imps/time bin) of nociceptive specific Sm neurons following control or $L_5$ thrust protocols

| Seconds | Control | | $L_5$ thrust | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| 10 | 0.39 | 1.23 | −0.28 | 0.80 |
| 60 | 4.75 | 3.65 | −0.93 | 4.31 |
| 120 | 6.36 | 4.42 | −0.88 | 7.72 |
| 180 | 3.35 | 5.56 | 6.64 | 6.16 |
| 240 | 11.63 | 7.39 | −18.39† | 7.13 |
| 300 | 0.98 | 9.03 | −5.43 | 9.22 |

Group: $F = 4.8$, $df = 1.5$, $p < 0.05$, post hoc † $p < 0.005$. Time (s): $F = 0.53$, $df = 5.5$

### Evoked noxious response

The mean change in Sm neuron response to a 10 s noxious stimulus applied before and after control and lumbar thrust was determined. Compared to control, inhibitory responses to noxious contralateral hindpaw stimulation were significantly attenuated after the $L_5$ thrust (Fig. 5; Table 2). Mixed neural responses were seen with noxious stimulation of the tail (inhibitory) and ipsilateral hindpaw (excitatory) following the $L_5$ thrust but these changes did not reach significance (Fig. 5). Figure 6 provides an example of a Sm neuron exhibiting a mixed response to tail and ipsilateral hindpaw stimulation after an $L_5$ thrust. It is possible that random bursts and/or time-related changes in

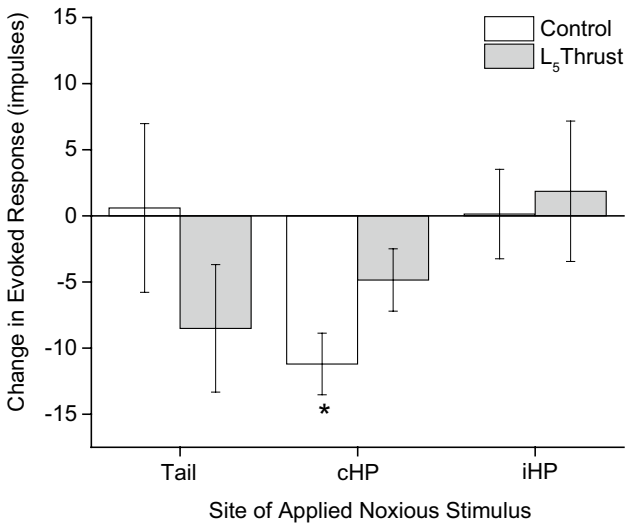


**Fig. 5** Evoked response. Mean changes (±SEM) in neural responses to 10 s pinch applied to three sites [tail, contralateral hindpaw (cHP), ipsilateral hindpaw (iHP) before and after control (no thrust)] or high velocity low amplitude $L_5$ thrust procedures. All submedius neurons exhibited greater than 20% increase over baseline activity to the first applied pinch stimulus at each site. (*$p < 0.05$)

resting baseline activity could have contributed to a mixed response (since the 10 s of resting baseline activity immediately preceding the pinch stimulus was subtracted from the evoked noxious response); however, no significant differences were found in pre–post mean baseline activity between the control and thrust protocols at these test sites.

## Discussion

The vast majority of nociceptive-specific Sm neurons in the current study had large (bilateral) receptive fields and exhibited a low to moderate spontaneous activity firing rate. This is in agreement with previous findings from a study involving 204 Sm neurons and urethane anesthesia (Kawakita et al. 1993). Kawakita et al. (1993) divided the Sm nucleus into four sub-regions and reported no significant differences in spontaneous activity between sub-regions nor between neuron responses recorded early or late in the experiment. We found that dynamic high velocity low amplitude thrusts similar to those applied in clinically delivered lumbar spinal manipulation produces a delayed and prolonged suppression of thalamic nociceptive-specific Sm neuron spontaneous activity. The physiological impact of this delayed but prolonged decrease of Sm activity is not currently known. Since widespread increases in thalamic spontaneous activity have been shown to occur in both acute and chronic pain conditions (Rinaldi et al. 1991; Hains et al. 2005; Fischer et al. 2009; Masri et al. 2009; Iwata et al. 2011) suppression of thalamic activity may play a role in spinal manipulation's clinical efficacy. Sustained changes in thalamic resting activity may in turn have neurophysiological consequences at the VLO or other efferent Sm connections as well. It is interesting to note that the delayed timing of this suppression of medial thalamic activity, ~3 min after the thrust delivery, coincides with the timing (<5 min) of reported mechanical/thermal hypoalgesic effects following clinically delivered spinal manipulative thrusts (George et al. 2006; Fernandez-de-las-Penas et al. 2007; Fernandez-Carnero et al. 2008; Bishop et al. 2011; de Camargo et al. 2011; Srbely et al. 2013). Decreased neural activation in other central structures following manual therapy intervention has been reported in both animal and human neuroimaging studies (Malisza et al. 2003a, b; Sparks et al. 2013). Decreased activity at thalamic and/or other key spinal/supraspinal pain modulatory centers may serve as a key neurobiological mechanism of spinal manipulation.

Studies using bilateral Sm electrolytic lesions indicate that Sm neurons are involved in supraspinal and/or spinal mediated inhibition of nociceptive input (Roberts and Dong 1994; Zhang et al. 1995). We observed a decrease of Sm neuron activity evoked by noxious contralateral hindpaw stimulation after the control procedure. This inhibitory Sm activity was attenuated after the $L_5$ thrust which suggests that lumbar thrusts may act to modulate nociceptive activity in higher pain centers. Despite Sm neurons typically having large (often bilateral) receptive fields, the

**Table 2** Mean changes and SEM of noxious-evoked response at three sites following control or $L_5$ thrust protocols among nociceptive-specific Sm neurons that demonstrated a minimum of 20% increase over baseline discharge on initial pinch stimulus at each site

| | Change in noxious-evoked activity (imps) | | | | | |
|---|---|---|---|---|---|---|
| | Tail ($n = 35$) | | Contra-HP ($n = 43$) | | Ipsi-HP ($n = 39$) | |
| | Mean | SEM | Mean | SEM | Mean | SEM |
| Control | 0.60 | 6.38 | −11.2* | 2.33 | 0.14 | 3.38 |
| $L_5$ thrust | −8.51 | 4.82 | −4.85 | 2.36 | 1.86 | 5.31 |
| | $t = 0.99$, $df = 34$, $p > 0.05$ | | $t = 2.3$, $df = 42$, *$p < 0.05$ | | $t = 0.34$, $df = 38$, $p > 0.05$ | |

There was a significant decrease in the contralateral hindpaw response after the $L_5$ thrust (* $p < 0.05$)

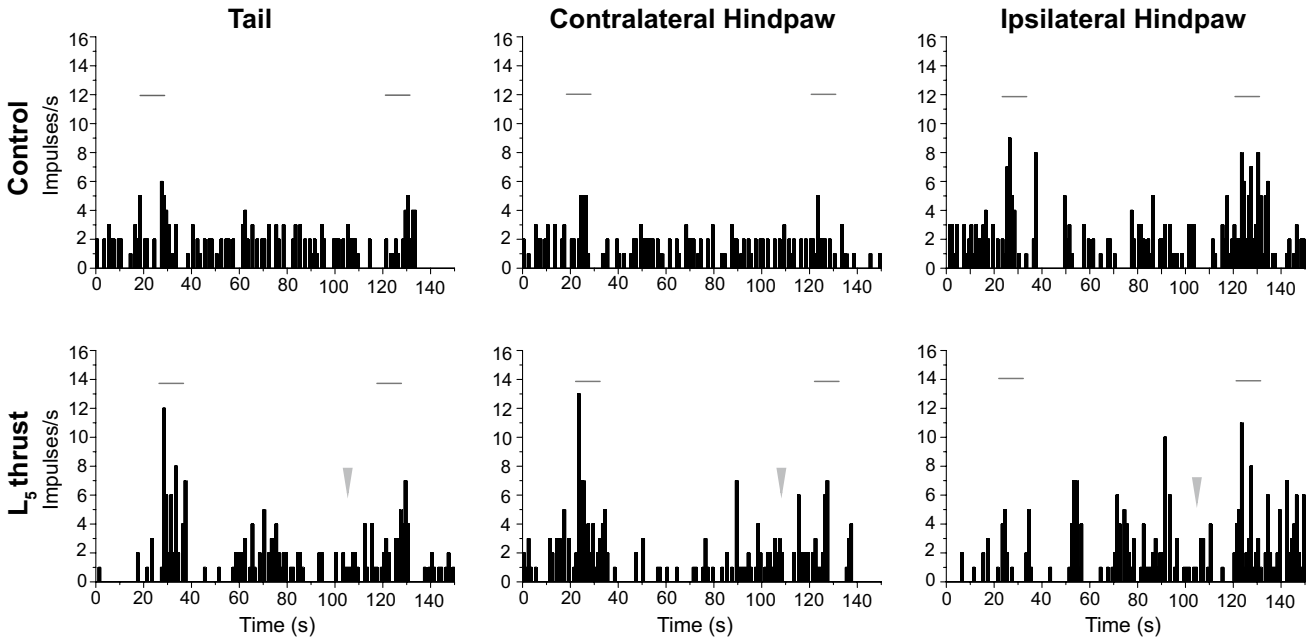


**Fig. 6** Example of Sm neuron response. Histogram of Sm neural responses (impulses/1 s bin) to noxious pinch at three sites (tail, contralateral and ipsilateral hindpaw) in both control and $L_5$ thrust protocols. *Gray horizontal bars* indicate noxious pinch application and arrowhead indicate time of $L_5$ thrusts. Note a decrease in tail and contralateral hindpaw post-thrust noxious response and an increase in ipsilateral hindpaw noxious response following an $L_5$ thrust. This neuron was located in the rostral Sm nucleus at 6.24 mm from the cortical surface

contralateral hindpaw was the only testing site to demonstrate a significant change following $L_5$ thrust. This is likely due to a greater preponderance (64%) of anatomically crossed ascending spinal projections to the Sm in the rat (Dado and Giesler 1990). While the changes did not reach significance, the $L_5$ thrust decreased Sm neuron response to tail pinch and increased Sm neuron response to ipsilateral hindpaw pinch. Sm neurons exhibiting inhibitory responses to noxious stimulation at one anatomical site and excitatory responses at another have been previously reported (Kawakita et al. 1993). These alternating nociceptive responses seen after $L_5$ thrust may be attributable to anatomical differences in peripheral nociceptor density, nociceptor sensitivity, and/or to the anatomical proximity of $L_5$ dorsal root ganglion cells to the lumbar thrust site compared to the sacral (S1–S4) dorsal root ganglion cells innervating the tail (Danneman et al. 1994; MacKenzie et al. 2015).

Despite both local and remote somatic hypoalgesic effects being associated with clinical spinal manipulative thrusts; the peripheral and/or central pathways, structures and mechanisms responsible remain unknown (Wright 1999; Bialosky et al. 2009a). Basic science (Vaillant et al. 2012; Reed et al. 2013, 2014b, 2015a, b; Onifer et al. 2015; Song et al. 2016) and clinical (Bishop et al. 2011; Nougarou et al. 2013; Sparks et al. 2013; Bialosky et al. 2014; Nougarou et al. 2014; Page et al. 2014) studies have begun to focus much greater attention on potential physiological mechanisms associated with non-pharmacological manual therapy interventions. A functional magnetic resonance imaging study investigating supraspinal activation related to noxious mechanical stimulation pre- and post-thrust spinal manipulation reported that while bilateral activation of the thalami, cerebellum, amygdala, periaqueductal gray, insular cortex, anterior cingulated cortex, somatosensory cortices, supplementary motor area, and premotor areas occurred with peripheral noxious stimulation; only the insular cortex demonstrated a significant relationship between pain reduction and post-spinal manipulation (Sparks et al. 2013). While this small ($n = 10$) clinical imaging study was unable to draw any definitive conclusions, it is interesting to note that the insula receives direct projections from medial thalamic nuclei (including the Sm) and that these nuclei are thought to be more involved with the affective and motivational aspects of pain which may in turn contribute to the efficacy of spinal manipulation and other integrative medicine interventions (Bushnell and Duncan 1989; Basbaum 2000; Jones 2007; Bialosky et al. 2009a).

## Conclusion

To our knowledge, this study is the first to investigate the effects of lumbar vertebra high velocity low amplitude thrusts on central spontaneous neural activity and noxiously evoked responses in the medial thalamus. The results indicate that lumbar vertebra thrusts cause a delayed and prolonged decrease in nociceptive-specific Sm neuron spontaneous activity. In addition, inhibitory responses to noxious contralateral hindpaw stimulation are attenuated following $L_5$ thrust. Additional acute and chronic pain studies need to be performed in the Sm as well as other thalamic subnuclei to determine if these neural changes occur more globally within the thalamus and/or impact nociceptive somatosensory processing at higher central centers.

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**Compliance with ethical standards**

**Ethical Approval** All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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