THE LOCAL FIELD POTENTIAL IN THE MEDIAL PREFRONTAL CORTEX IN RESPOSE TO PERIPHERAL NERVE STIMULATION

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Abstract

THE LOCAL FIELD POTENTIAL IN THE MEDIAL PREFRONTAL CORTEX IN RESPOSE TO PERIPHERAL NERVE STIMULATION

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Nociceptive stimuli can activate peripheral nociceptors to produce nociceptive signals which can be projected to the spinal cord and further up to the thalamus and many other cortical and subcortical areas through ascending pathways. Nociceptive information can be processed in various brain areas (e.g., somatosensory cortex and anterior cingulate cortex); it can change activities in those brain areas and eventually result in morphological changes following long-term stimulation. The medial prefrontal cortex (mPFC) has been proven to be involved in higher cognitive functions and emotional processing. It receives projections from brain areas that are involved in nociception. Morphological changes of the mPFC happened in chronic pain patients and rats with neuropathic pain, and decreased single neuronal activity has been observed in rats after the induction of arthritic pain. In this study, both single cell activity of spinal cord dorsal horn (DH) and the local field potential (LFP) of the mPFC were investigated in response to peripheral graded electrical stimulation of L5 spinal nerve (SN) by a customized wireless module (10Hz, 1ms, 5s, from 0.1v to 5v with 0.5v increment). It was found: (1)

The DH neuronal activity was significantly increased by L5 SN stimulations equal to or higher than 0.5v ($p < 0.05$), intensity-dependently. Significant after-discharge was also observed at high-intensity stimulations from 3.5v to 5v. Electrical stimulation at 1v or higher showed similar DH response to phase I response after formalin injection. (2) In anesthetized animal, LFP was reduced bilaterally in mPFC by L5 SN stimulation, with slightly different pattern in each side. The inhibition became significant starting at 1v for contralateral and 3v for ipsilateral mPFC. Similar inhibition of LFP was observed in mechanical (pinch) and chemical (formalin injection) nociceptive stimulation. (3) The inhibition of LFP in mPFC by L5 SN stimulation and formalin injection was not observed in the freely moving animal. In conclusion, the electrical stimulations of L5 SN at intensities that induced comparable DH response as formalin injection reduced the LFP in mPFC under anesthesia. The inhibition was similar to that induced by mechanical and chemical noxious stimulus. However, such mPFC inhibition was not observed in freely moving animal which might be due to additional emotional and cognitive processing during awake state that has masked the effect.

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Chapter 1

Introduction

Noxious stimuli activate nociceptors at periphery to produce nociceptive signals which can be transmitted to the spinal cord, and further up to the thalamus and many other cortical and subcortical areas through ascending pathways. There are several pathways through which nociceptive signals reach different brain areas (Basbaum & Jessell, 2000). The spinothalamic tract passes nociceptive signals to the thalamus through anterolateral white matter on the contralateral side of the spinal cord, then from thalamus signals will be further passed on to different brain areas. The spinoreticular tract carries nociceptive signals from spinal cord to reticular formation and thalamus through anterolateral quadrant spinal cord. The spinomesencephalic tract sends nociceptive information to the mesencephalic reticular formation and periaqueductal gray matter, to parabrachial nuclei, then eventually reaches amygdala. This spinomesencephalic pathway mainly contributes to the affective component of pain. The cervicothalamic tract arises from the upper two cervical segments of the spinal cord, and project to thalamus.

Along all the pathways, nociceptive signals are processed and encoded at various levels from the nociceptors at the periphery to the supraspinal cortical areas. In the past, a lot of effort has been focused on the peripheral mechanism of pain. During recent decades, more and more attention has been directed to the cortical processing of pain (Tracey & Mantyh, 2007). It is well accepted that at cortical level, the sensory discriminative properties of nociception were encoded in primary somatosensory cortex (S1) which receives input from spinothalamic tract (R Melzack & Casey, 1968). While the affective and motivational component associated with pain is processed in limbic system and other brain areas receiving information from spinoreticular and spinomesencephalic pathways (Melzack & Casey, 1968). The first section of the introduction summarized some findings of brain areas affected by pain.

1.1 Activity and Morphological Changes in Brain Areas to Pain

1.1.1 Activity Changes in Brain Areas to Pain

With the development of brain imaging techniques, researchers were able to study the activities in various brain areas in response to different types of nociceptive stimuli. Before the use of functional magnetic resonance imaging (fMRI) became widespread, researchers used postron emission tomographic (PET) to scan the cerebral blood flow of the brain of subjects receiving IV injection of tracers which are radioactive substance that can attach to glucose. Glucose is the primary fuel of the brain. Active area of the brain consumes more glucose as compared to the inactive areas. This measurement reflects the amount of brain activity in various regions of the brain. S1, S2 (secondary somatosensory cortex), thalamus, anterior cingulate cortex, insula showed relatively consistent activation to nociceptive input (Casey et al., 1994; Coghill et al., 1994; Coghill et al., 2014; Derbyshire et al., 1997; Hsieh et al., 1996; Iadarola et al., 1998; Jones, Brown, Friston, Qi, & Frackowiak, 1991; Talbot et al., 1991). Animal study of pain model showed similar activated brain areas (Mayer, Price, College, & Commonwealth, 1993). Other areas such as primary/supplementary motor area, cerebellum, periaqueductal grey, putamen, lentiform nucleus, hypothalamus, prefrontal cortex, hippocampus, were only activated in some of those studies. This might be due to the different noxious stimuli applied and different procedures. Later, fMRI studies found similar results (Becerra et al., 1999; Bingel et al., 2002; Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002). But in chronic back pain patients, the scenario was different from the acute pain to some extent. In response to experimental pain, chronic pain patients involved PFC more frequently, while normal subjects involved ACC more frequently. In addition, chronic clinical pain are often associated with decreased baseline or stimulus releated activity in thalamus (Apkarian, Bushnell, Treede, & Zubieta, 2005).

1.1.2 Morphological Changes of Brain Areas to Pain

Beside the observed activity changes in multiple brain areas for both acute and chronic pain, morphological changes have also been noticed in pain patients. Decreased gray matter has been found in patients with various type of pain, such as chronic back pain (Apkarian et al., 2004; Seminowicz et al., 2011), headache (Absinta et al., 2012; Obermann et al., 2009; Schmidt-Wilcke et al., 2005), migraine (Rocca et al., 2006), fibromyalgia (Burgmer et al., 2009; Kuchinad et al., 2007). The decrease of gray matter seems to correlate with the duration of pain (Schmidt-Wilcke et al., 2005). And it can be reversed in some cases if pain was successfully treated (Seminowicz et al., 2011). Common areas with reduced gray matter across studies are frontal cortex (especially dorsolateral prefrontal cortex, sometimes orbital and medial prefrontal cortex), ACC, insula, areas in temporal lobe including parahippocampal gyri, and the superior temporal gyrus. Other areas dependent on the type of chronic pain and disability the patients have may also show decreased gray matter, such as thalamus, amygdala, and motor cortex, cerebellum, etc. Although the majority of the studies found decreased gray matter in pain patients, few studies found areas with increased gray matter (DaSilva, Granziera, Snyder, & Hadjikhani, 2007; Rocca et al., 2006). Taken together, these results support the proposition that pain can change the activity in higher level brain areas, and if it is persistent, it will eventually result in long-term change of the morphology of those brain areas.

1.2 Purpose of This Study

Although activities and morphological changes caused by pain have been observed in certain brain areas, the detailed profile of the involvement of some brain areas in pain processing remains unexplored. Morphological changes of the medial prefrontal cortex (mPFC) has been found in rats with spared nerve injury (SNI) (Metz, Yau, Centeno, Apkarian, & Martina, 2009). But very few studies have investigated the electrophysiology profile of mPFC except one study that found the deactivation of the mPFC by single unit recording in response to arthritis induction by intra-articular injection of kaolin/carrageenan (Ji & Neugebauer, 2011; Ji et al., 2010).This study aimed to investigate the LFP response profile of mPFC to a wide range of sensory input by peripheral nerve stimulations at different intensities.

1.2.1 Medial Prefrontal Cortex (mPFC)

The mPFC is one portion of the prefrontal cortex besides the orbital and lateral prefrontal cortices. It constitutes the major portion of the medial wall of the hemisphere, and is anterior and dorsal to the genu of corpus callosum. It consists of four main divisions which include the medial agranular, the anterior cingulate, the prelimbic, the infralimbic cortices (Hoover & Vertes, 2007). The mPFC has been found to be involved in diverse functions, including basic motor behaviors, such as oculomotor control, or higher cognitive functions, such as memory and decision making. The dorsal part of mPFC (medial agranular and anterior cingluate) are implicated in various motor behaviors, while the ventral regions of mPFC are invovled more in emotional, cognitive processes (Heidbreder & Groenewegen, 2003).

It has been shown that prefrontal areas are involved in processing of pain (Apkarian et al., 2005; Ochsner et al., 2006; Tracey & Mantyh, 2007). Based on the anatomical afferent projections to the mPFC, the mPFC receives projections from brain areas involved in nociception (Hoover & Vertes, 2007). The dorsal part of the mPFC, mainly agranular cortex and dorsal antierior cingulate, receives predominantly sensorimotor input by projections from widespread areas of the cortex for all sensory modailites. The main sources of afferent projections to the ventral part of the mPFC, PL and IL, are from some subcortical structures, such as basal nuclei of amygdala, the midline thalamus, monoaminergic nuclei of the brainstem, hippocampus, and other cortical areas such as orbitomedial prefrontal, agranular insular, perirhinal and entorihinal cortices. Of these brain regions that provide input to the mPFC, some are recipients for nociceptive input, such as amgydala, midline thalamus, etc. Therefore the nociceptive information may eventually reach the mPFC.

The mPFC has also been implicated in stress response. Several studies have found that daily restraint stress (3 h per day) could reduce apical dendritic branches, terminal branches and dendritic spines of pyramidal neurons in the mPFC(Cook & Wellman, 2004; Radley et al., 2006). And daily injection of corticosterone resulted in the similar morphology changes in mPFC (Brown, Henning, & Wellman, 2005). The response of the mPFC to stress can be very sensitve, because vehicle injection itself in control group resulted in smilar but less prounced changes in morphology (Brown et al., 2005).

Pain is a ‘real’ stressor that can present a genuine homeostatic challenge (Herman et al., 2003). Given that mPFC can indrectly receive nociceptive input and is very sensitive to stress, pain might have a great influence on the mPFC.

1.2.2 Cuff Electrode Peripheral Nerve Stimulation

Peripheral nerve stimulation has been originally established to treat pain. It is based on the gate control theory proposed by Melzack and Wall in 1965 that input from large diameter afferent fibers will inhibit the information carried by small diameter afferent fibers, thereby blocking pain perception. It was found in experiment that low electrical stimulation of peripheral nerve via subcutaneous electrode could produce temporary pain relief (Wall & Sweet, 1967). This led Sweet to perform the first permanent implantation of a peripheral nerve electrode in an attempt to obtain long-term pain relief (Sweet, 1976). However, when the intensity of stimulation is big enough to activate small fibers, it can result in pain.

In this study, I plan to implant cuff electrode around L5 spinal nerve (SN) and stimulate the nerve with graded intensity from 0.1v to 5v using our custom-designed wireless stimulator (Figure 1.1). A nerve fiber’s excitation threshold is dependent on the type of fiber (Panizza et al., 1998) and its diameter (Blair & Joseph, 1933; McNeal, 1976). It has been approved that large fibers were recruited before small diameter nerve fibers by electrical stimulation (Blair & Joseph, 1933). It can be expected that the large thickly myelinated Aβ fibers are excited before Aδ and C fibers, and C fibers are the last one to become excited. So, at the lowest intensity, the electrical stimulation may not activate any nerve fibers, or activate few big fibers. More and more small fibers are recruited by the electrical stimulation as the intensity increases.

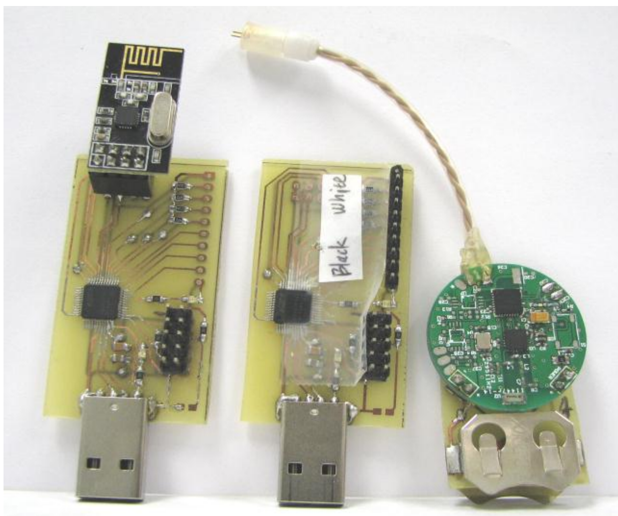

Figure 1.1. Custom-designed wireless stimulation module.

The two USB dongles on the left were connected to the laptop to deliver the stimulation command to the stimulator on the right, which was connected to the implanted cuff electrode.

Parameters that have been used to artificially stimulate nerve fibers vary across studies. Some studies used certain current (Hathway, Vega-Avelaira, Moss, Ingram, & Fitzgerald, 2009; Koga et al., 2005; Vatine, Argov, & Seltzer, 1998), while others used certain voltages (Liu, Morton, Azkue, Zimmermann, & Sandkühler, 1998). Different pulse width and frequency were also applied in different studies. Despite the differences in electrical stimulation parameters across studies, there are some general patterns. Low frequency arranging from 0.5 Hz to 10 Hz has been used to activate C fibers (Hathway et al., 2009; Koga et al., 2005; Vatine et al., 1998). Higher frequency can be used to recruit Aδ and Aβ fibers. The intensity (either current or voltage) used to excite nerve fibers is inverse to its diameter. There is no clear cut in different simulation parameters that recruit different fibers without special techniques. The stimulations that recruit small fibers can also excite big fibers (Hathway et al., 2009; Koga et al., 2005; Vatine et al., 1998), but tactile sensation won't be perceived when painful sensation is produced at the same time (Koga et al., 2005). Given all those information, the electrical stimulation parameters in this particular study is set at frequency of 10 Hz (the lowest frequency can be set in our custom-designed wireless stimulation module), pulse width of 1 ms, duration of 5s from 0.1v, 0.5v, 1v, up to 5v (the highest voltage can be set in the stimulation module) with 0.5v increment.

1.2.3 Specific Aims

This study aimed to investigate the LFP in the mPFC in response to L5 SN stimulation at different intensities. As it is mentioned above that different stimulation intensities recruit different fibers, with graded intensity of electrical stimulation, more and more small fibers are expected to be recruited. There are three specific aims in this study. The <u>first specific aim</u> is to determine the profile of dorsal horn (DH) response to peripheral SN stimulation and if the DH response is comparable to that induced by natural noxious stimuli. It is *hypothesized* that the SN stimulation can induce the DH neuronal activity which will increase with the graded stimulations. The response at high-intensity stimulation of SN may be comparable to the response caused by natural noxious stimuli, such as formalin injection. The second specific aim is to investigate how L5 SN stimulations change the LFP in the mPFC in anesthetized animal. It is *hypothesized* that SN stimulation can decrease the LFP in the mPFC at certain intensities. This effect was further confirmed by applying natural noxious stimuli. The third specific aim is to investigate how L5 SN stimulations change the LFP in the mPFC in freely moving animal. Similar changes in the LFP of mPFC are expected in freely moving animal as it is in anesthetized animal. Differences are also anticipated because of the difference in the brain between anesthetized state and awake state with additional cognitive and emotional processing going on.

Chapter 2

Methods

All procedures used in this study were approved by the Animal Care and Use Committees of University of Texas at Arlington and followed the guidelines for the treatment of animals of the International Association for the Study of Pain (Zimmermann, 1983).

2.1 Extracellular DH Single Cell Recording

The purpose of this experiment was to determine the response profile of DH neuron to electrical SN stimulation with different intensities.

2.1.1 Subjects

Seven male Sprague-Dawley rats (200 ± 16 d, 454 ± 37 g) were involved in this experiment. All animals were from animal breeding colony of the University of Texas at Arlington.

2.1.2 Animal Preparation

The induction of anesthesia was induced by an intraperitoneal (i.p.) injection of sodium pentobarbital (50 mg/kg i.p.). The depth of anesthesia was confirmed by the absence of the withdrawal responses to tail pinch and toe pinch. A second i.p. injection might be applied depending on the specific situation. Continuous administration of anesthesia (5 mg/ml pentobarbital at rate of 1.0 ml/h, i.v.) during recording was accomplished by a catheter placed in the jugular vein. Respiratory rate was monitored throughout surgery and recording process. Tracheotomy was also performed in case ventilation was needed.

2.1.3 DH Recording

A laminectomy was performed to expose 4-5 cm of spinal cord over the lumbosacral enlargement area. An intact vertebra was exposed at each end of the exposed lumbar segment for stabilization purpose of the spinal cord on the stereotaxic frame. Rat was in a prone position on the stereotaxic frame with the head and spinal cord stabilized to reduce any movement during the recording. A tungsten recording electrode (FHS, Brunswik, ME, 10-12 Megohm) was dropped to the target area (L5 entry zone of the spinal cord). This recording electrode was connected to the CED1401 recording system which sent signals to be displayed on the oscilloscope and recorded on computer. Data were recorded and analyzed by Spike 2 software. Wide dynamic range (WDR) neurons were recorded and identified based on their responses to graded mechanical stimuli (brush, pressure and pinch) applied at the receptive field of plantar surface of the hind paw. Brush was applied by a small hair brush; pressure and pinch were applied by a venous bulldog clamp of 6 cm long and an arterial bulldog clamp of 3 cm long respectively. Activities of DH neurons to brush, pressure and pinch followed by electrical SN stimulations at different intensities (5s, 1ms, 10Hz at 0.1v, 0.5v, 1v…… up to 5v with 0.5v increment) were recorded. For the last cell of recording of each rat, 50 µl of 3% formalin was injected to the plantar surface of the left hind paw after electrical stimulations, and another 15 to 20 min recording was made before the end of the experiment.

2.1.4 L5 SN Stimulation

A longitudinal incision at the lower lumbar/upper sacral level (about 3 cm long, and 1 cm off the midline) on the left side of the back around the hip area was made to expose the paraspinal muscles. Using a small curved scissor, the paraspinal muscles were removed to expose the L6 transverse process which covers the ventral rami and the L4 and L5 SN. The connective tissue that covers the transverse process was cleaned using a small scraper and L6 transverse process was removed by a small rongeur. The L5 spinal nerve was easier to spot and close to the body of vertebrae, while the L4 spinal nerve was further away from the body of vertebrae and towards the side. Two soft wires (around 7 cm long, Cooner Wire AS 155-36) with middle part and two ends exposed were placed underneath the L5 spinal nerve guided by a curved needle (see Figure 2.1 for a schematic illustration of the placement of the wires). After confirmed that the exposed middle part was touching the nerve, the portion of the wire close to the incision of the muscle was sowed to the fascia layer of the cut to reduce any influence by the movement of the external part of the wire.

The end of two wires was connected to the custom-designed wireless stimulation module (Figure 2.1). Two USB dongles were plugged to a laptop with the stimulation software. Two coin batteries of 3 volts were placed on the module before stimulation. Stimulation parameters were 1 ms, 10 Hz at 0.1v, 0.5v, 1v…… up to 5v with 0.5v increment.

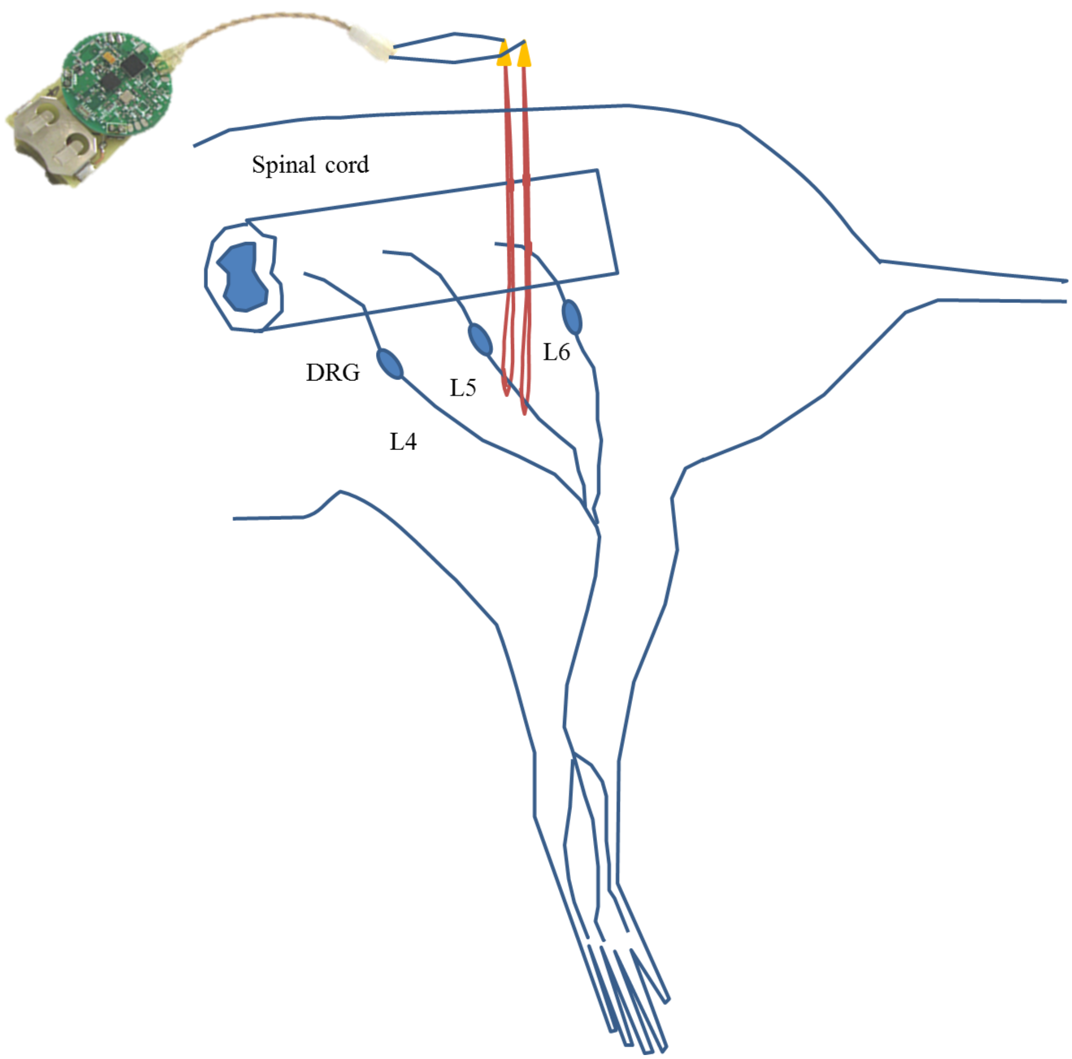

Figure 2.1. Illustration of cuff electrode stimulation.

The two red wires that go underneath of the L5 SN are cuff electrodes implanted and connected to the wireless stimulator.

2.1.5 Data Analysis

The recorded raw wave form data of action potential were analyzed offline using spike2. V7 software. Spikes were sorted based on their amplitude and shape. Differences in the firing rate were tested by repeated measure ANOVA followed by LSD post-hoc test. $P < 0.05$ was considered significant.

2.2 The LFP Recording of mPFC in Anesthetized Animal

2.2.1 Subjects

Fourteen male Sprague-Dawley rats (183 ± 5 d, 459 ± 44 g) were involved in the SN stimulation group. For mechanical stimulation and formalin injection group, eight male Sprague-Dawley rats (181 ± 10 d, 424 ± 53 g) for contralateral recording and eight (181 ± 10 d, 420 ± 61 g) for ipsilateral recording were included. All animals were from animal breeding colony of the University of Texas at Arlington.

2.2.2 Animal Preparation

The induction of anesthesia was induced by an intraperitoneal (i.p.) injection of sodium pentobarbital (50 mg/kg i.p.). The depth of anesthesia was confirmed by the absence of the withdrawal responses to tail pinch and toe pinch. A second i.p. injection was applied depending on the specific situation. Continuous administration of anesthesia (5 mg/ml pentobarbital at rate of 1.0 ml/h, i.v.) during recording was accomplished by a catheter placed in the jugular vein. Respiratory rate was monitored throughout surgery and recording process. Tracheotomy was also performed in case ventilation was needed

2.2.3 LFP Recording

Animal was placed on the stereotaxic frame in a prone position. Head was stabilized with ear bars and a mouth piece. The position of the head was adjusted so that it was as straight and flat as possible. Craniotomy was performed to drill a role on the skull above the target area, the prelimibic (PL) area of the mPFC. The coordinates for the target area were 3 to 3.7 mm rostral to the bregma, 0.5-0.8 mm lateral to the midline, 3-3.5 mm below the dura membrane. The field potential recording was accomplished by using our customized wireless recording module designed by Zuo and Wang (Figure 2.2). Two dongles were connected to the laptop which has the recording software to receive the incoming field potential signal. A twisted bipolar electrode (PlasticsOne MS 303-1-B-SPC ELECT SS 2C TW .010in) was inserted into the target area and connected to wireless recording module. The recording terminal of the module as indicated by 1 in Figure 2.2 was connected to the recording electrode; both reference terminal as indicated by 2 and grounding terminal as indicated by 3 in Figure 2.2, were clamped to the skin on each side of the head. Bilateral LFP recording was performed on the same rat with a pseudo-randomized order.

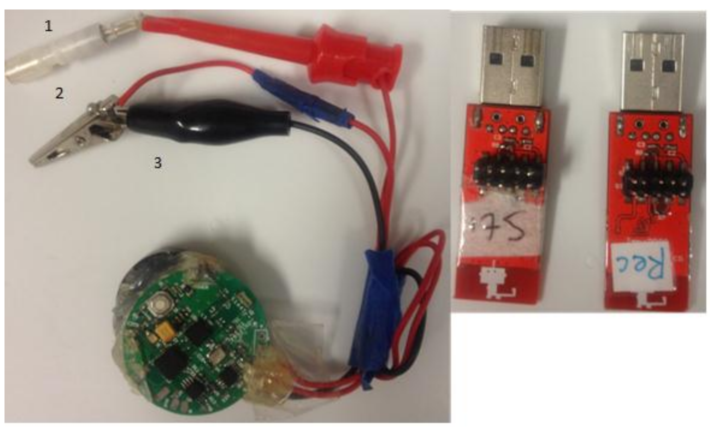

Figure 2.2. Local field potential recording device.

The module on the left is the recording module that was connected to the implanted electrode in mPFC. 1: recording terminal connected to the implanted electrode; 2: reference terminal; 3: grounding terminal. The two USB dongles on the right were plugged to the laptop to receive the LFP signals from the recording module.

2.2.4 L5 SN Stimulation

The surgical preparation and stimulation was the same as described in Section 2.1.4.

2.2.5 Mechanical & Formalin Injection

The effect of mechanical and chemical noxious stimuli on the mPFC LFP was tested on a different group of sixteen rats with eight rats for each side. Mechanical stimuli were applied before formalin injection in the order of brush, pressure and pinch. Each mechanical stimulus lasted for 5 s with 1 min interval between each. Five minutes after the last mechanical stimulus, 50 µl of 3% formalin was injected into the plantar surface of the left hind paw, and another 45 min recording was made before the end of the experiment.

2.2.6 Histology

At the end of the recording, animals were euthanized by overdosing of pentobarbital. Their brains were extracted and stored in 10% formaldehyde for at least 24 hours before changing to 30% sucrose. The brains were sectioned at 80 µm using microtome after they have sunk down to the bottom of the vial with sucrose solution. Brain slices were stained with thionine and observed under microscope to determine the placement of the tip of the electrode.

2.2.7 Data Analysis

The saved data in text file were imported into CED Spike 2.7V software as raw waveform at sampling rate of 4096 Hz. Power spectrum analyses were performed for 5 s before, 5 s during and 5s after the electrical and mechanical stimulation; and for 5 seconds before formalin injection and 5s at the beginning of every 5 min immediately after injection (Figure 2.3 A). The Power of frequencies from 1 to 100 Hz was included in the analyses, except the power of frequencies at 50, 51, 52 caused by the 50 Hz noise in the recording (Figure 2.3 B). The results of power spectrum analysis in histogram (Figure 2.3 B) were then exported into an Excel file as individual power number for each frequency. The overall power from 1 to 100 Hz and the power for each frequency band (delta < 4 Hz, theta 4-7 Hz, alpha 8-12 Hz, beta 13-30 Hz, gamma 30-100 Hz) were statistically analyzed respectively. Repeated measure ANOVA followed by LSD post-hoc test was used to test the activity changes in target area during and after all manipulations. $P < 0.05$ was considered significant.

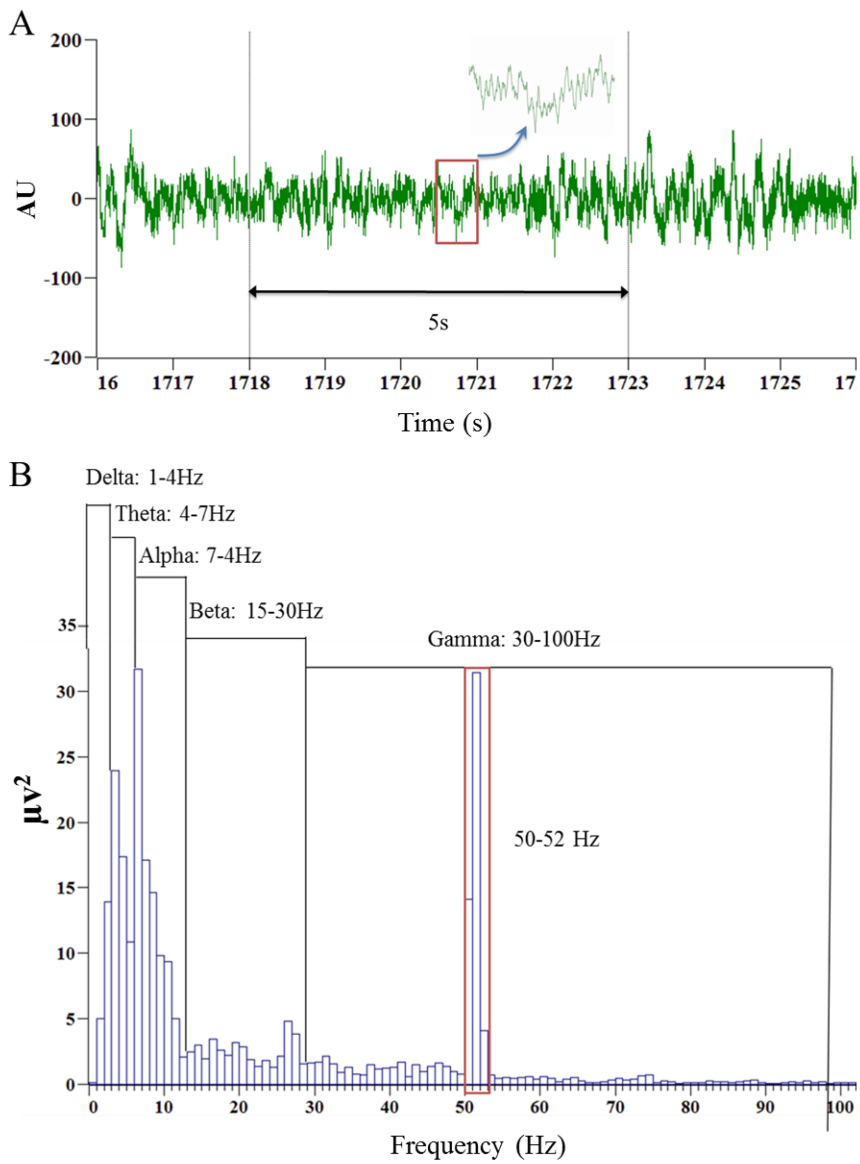

Figure 2.3. Power spectrum analysis.

AU: arbitrary unit. A: an example of 5 s of the raw trace taken for power spectrum analysis. B: The results of the power spectrum analysis for the 5s raw trace in A; the power from 50 to 52 Hz (highlighted in red square) caused by noise was deleted in statistical analysis .

2.3 The LFP Recording of the mPFC in Freely Moving Animal

2.3.1 Subjects

Nine male Sprague-Dawley rats (181 ± 7 d, 436 ± 38 g) were involved in the this experiment. All animals were from animal breeding colony of the University of Texas at Arlington.

2.3.2 Electrode Implantation

The induction of anesthesia was induced by an intraperitoneal (i.p.) injection of sodium pentobarbital (50 mg/kg i.p.). The depth of anesthesia was confirmed by the absence of withdrawal responses to tail pinch and toe pinch. A second i.p. injection might be applied depending on the specific situation. Respiratory rate was monitored throughout surgery. Animal was placed on the stereotaxic frame in a prone position. The head was stabilized with ear bars and a mouth piece, and was adjusted that it was as straight and flat as possible. Craniotomy was performed to drill five holes on the skull (Figure 2.4 A). Twisted bipolar electrodes (Plastics One MS 303-1-B-SPC ELECT SS 2C TW .010in) were inserted into the target area bilaterally through the holes anterior to bregma (Figure 2.4 A: 1 & 2). In order to avoid damaging the big sinus at the midline, electrodes were inserted to reach the target area at 20^o angle (Figure 2.4 B). The coordinates for the target area at 20^o angle were 3 - 3.7 mm rostral to the bregma, 1.8 - 2 mm lateral to the midline, 3-3.2 mm deep from the dura membrane. Three tiny anchor screws (Plastics One Screw 0-80X1-16) were inserted into the other three holes (Figure 2.4 A: 3, 4 & 5) to grab the cement with the skull and built the base that held electrodes. Two additional small wires attached to the screws above cerebellum area (Figure 2.4 A: 4

& 5) served as connecting points for reference and grounding terminal. After all electrodes and screws were in position, bone cement powder (Codman cranioplastic) was dissolved in methyl methacrylate (Sigma-Aldrich M55909) and applied to the skull to cover everything. Bone cement was reshaped to make the edge smoother after it became less fluid. The skin cut was stapled after the bone cement became completely dry and hard. Animals were left under the heating lamp till they woke up. All animals were given one week to recover before the LFP recording.

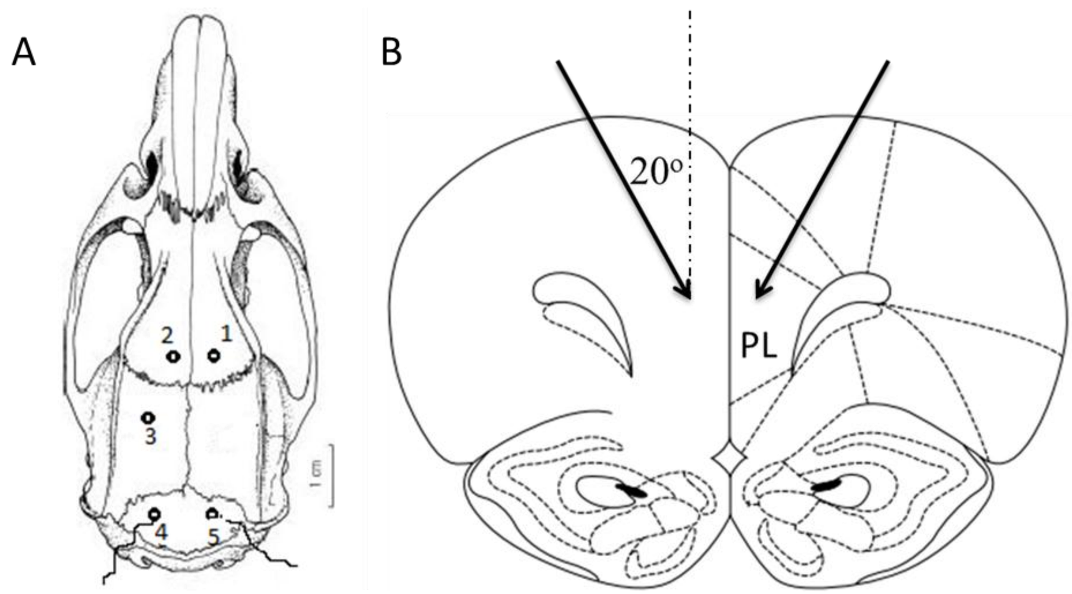

Figure 2.4. Illustration of the placement of recording electrodes and anchor screws (modified from Paxinos & Waston, 1998).

A: Diagram of the position for electrodes and screws. 1 and 2 are positions for electrodes; 3, 4 and 5 are positions for screws. Black lines coming out from screw 4 and 5 are wires used for reference and grounding during the LFP recording. B: Diagram of the electrodes reaching the target area at 20^{o} angle.

2.3.3 Cuff Electrode Implantation Around L5 Spinal Nerve

After the implanted wires were positioned underneath L5 SN with exposed middle part touching the nerve (same procedure described in Section 2.1.4), the inner muscle layer was sutured and outer skin cut was stapled to close the wound at the end of the implantation. Animals were left under the heating lamp till they woke up. All animals were given one week to recover before the SN stimulation.

2.3.4 LFP Recording

In order to connect modules to implanted electrodes on animal, animal was anesthetized using isoflurane (3% isoflurane in 100% oxygen for induction and 2.5% isoflurane for maintenance, adjustable base on the depth of anesthesia). A customized backpack was put on the rat to carry the wireless recording and stimulating module (Figure 2.5). The wire coming out from the wireless recording module was connected to the implanted electrode in the PL, and the wireless stimulating module was connected with the end of implanted cuff electrode wires around L5 spinal nerve. After animal woke up, the LFP in PL was recorded in response to the electrical stimulation of L5 SN at different intensities (1 ms, 10 Hz for 5s at 0.1v, 0.5v, 1v…… up to 5v with 0.5v increment). Each stimulation lasted for 5s with 1 min interval between stimulations. The stimulation was stopped at one or two more stimulations after rat manifested vocalization, since the animal was extremely stressed after they showed vocalization. If the animal didn’t show any vocalization, then the stimulation continued to increase to the highest voltage (5v) that the wireless stimulator can deliver. Bilateral recording of LFP was performed on the same rat with pseudo-randomized order. At the end after cuff stimulations, a 50 µl 3% formalin was made to the plantar surface of the left hind paw followed by another 45 min recording.

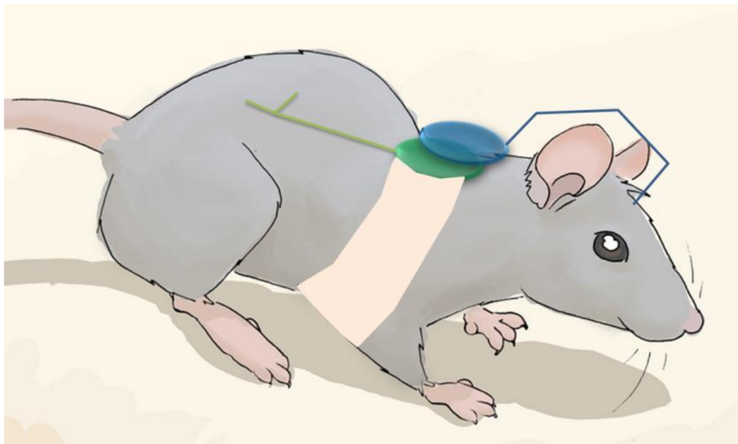

Figure 2.5 Animal carrying stimulating and recording module.

The blue one on top is wireless recording module, and the green one below is wireless stimulating module.

2.3.5. Mechanical Paw Withdraw Threshold (MPWT) Testing

Right before and one week after cuff electrode implantation, animals were tested for MPWT to determine if the surgery caused any pain condition per se, such as neuropathic pain. Before the testing, animals were habituated in the chamber for 15 min. Von Frey filaments at different forces were used to poke the plantar surface of hind paw, and the force at which point animal withdrew the paw was recorded to calculate the mechanical pain threshold. Three trials were performed at each time.

2.3.6 Histology

At the end of the recording, animals were euthanized by CO_2. The histology procedure was the same as described in Section 2.2.6.

2.3.7. Data Analysis

The data analysis for LFP was the same as the procedure described in Section 2.2.7. Average MPWT scores were calculated according to the method proposed by Dixon (1980); and two-way repeated measure ANOVA followed by LSD posthoc was used to test any differences, $p < 0.05$ was considered significant.

Chapter 3

Results

3.1 DH Single Cell Neuronal Responses

3.1.1. SN Electrical Stimulation Increased DH Neuronal Response

To determine the DH response profile induced by electrical stimulation of L5 SN, a total of 42 cells from 7 rats were included in analysis. Wide dynamic range (WDR) neurons were identified based on their graded response to brush, pressure and pinch (Figure 3.1 A). The DH responses of 5 s before stimulation, 5 s during stimulation and 5 s immediately after stimulation were analyzed. The DH neuronal activity increased gradually with the graded electrical stimulations of L5 SN (Figure 3.1 B). Significant after-discharge was mostly observed at high-intensity stimulations from 3.5v to 5v. The DH response seems to increase in a stepwise fashion. It increased gradually from 0.1v to 1v, then stayed there till the response was increased again by 2.5v, 3v; the response reached plateau at 4v stimulation (Figure 3.1 B).

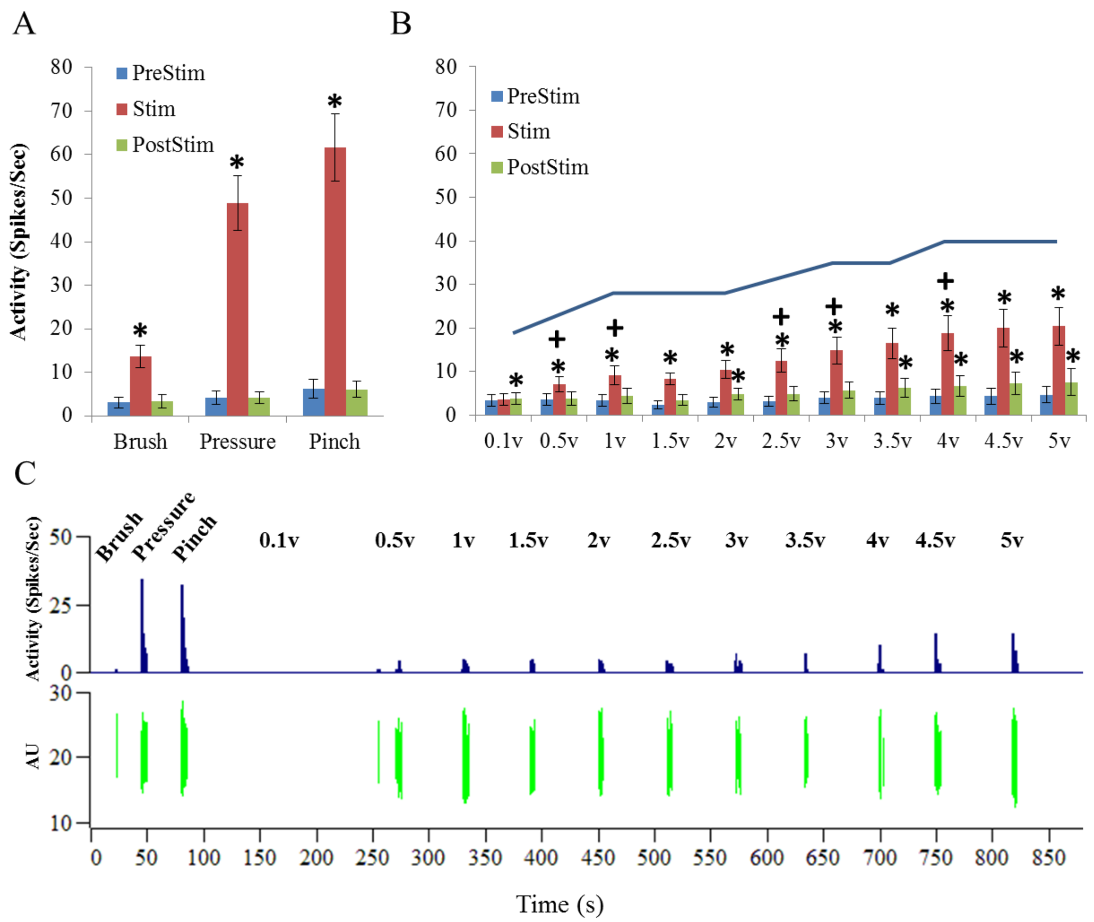

Figure 3.1. DH neuronal responses to mechanical stimulations of the left hind paw and SN electrical stimulations (10 Hz, 1 ms, 5 s from 0.1v to 5v). PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. A: DH responses to mechanical stimuli of brush, pressure and pinch (n = 42); B: DH responses to SN electrical stimulations (n = 42). C: Representative DH neuronal responses of a single cell to mechanical and electrical stimulations. The upper trace is the histogram indicating the firing rate and the lower trace is the recording of raw action potentials. *: response significantly differs from the pre-stimulation period. +: response significantly differs from the previous response during stimulation.

3.1.2. Formalin Injection Increased DH Neuronal Response

DH response to formalin injection was analyzed for 5 s before the injection, 5s during the injection, 5s after injection (first phase) and 5s starting at 20 min after the injection (second phase). The response of 5s during injection was not taken as the response for the first phase, because other sensations such as touching of the paw were present beside the formalin injection per se. The second phase was taken 20 min after the injection according the approximate starting point of the second phase in other study (Dubuisson & Dennis, 1977). The DH response increased significantly during injection and phase I of formalin injection (Figure 3.2). The response of phase I didn’t significantly differ from the response caused SN stimulation of 1v or higher (Figure 3.1 B).

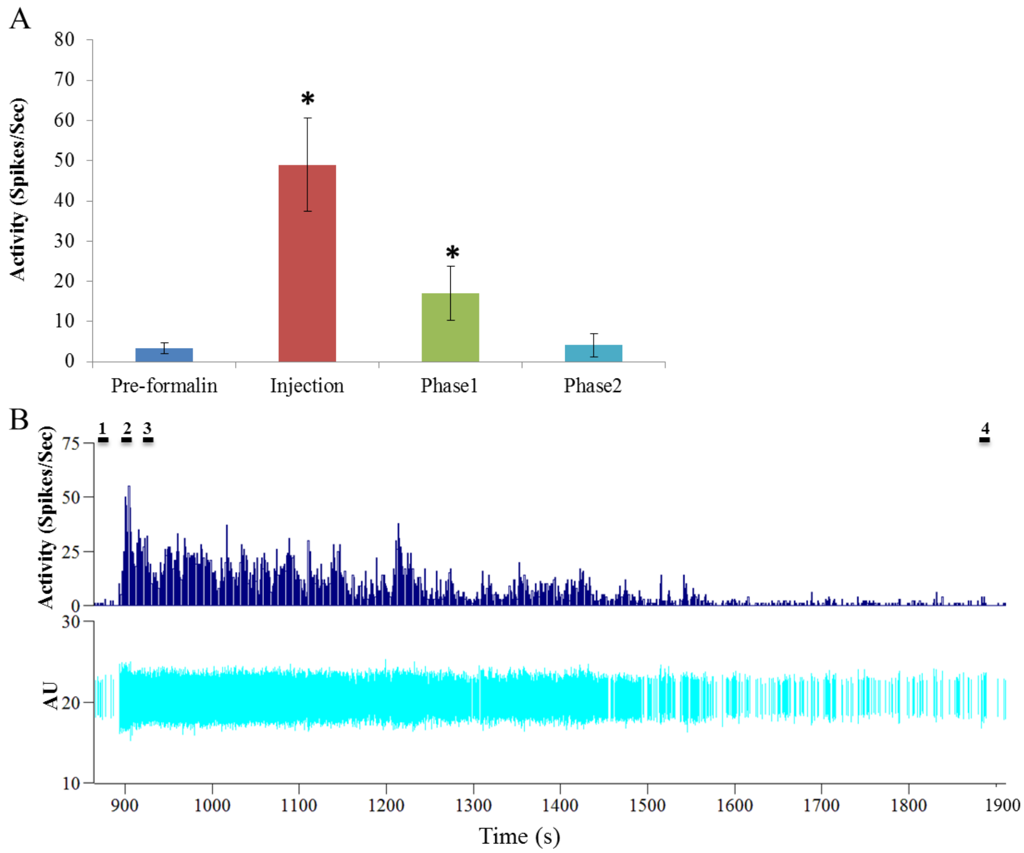

Figure 3.2. DH neuronal responses to formalin injection.

A. Summarized DH responses during pre-formalin, injection, phase I and phase II period (n=15). B. Typical response of a DH neuron to formalin injection. The upper trace is the histogram representing the firing rate of the neuron and the lower trace is the recording of raw action potentials. The thick black bars above the histogram indicate the four different periods taken for analysis. 1: pre-formalin; 2: injection; 3: phase I; 4: phase II. *: response significantly differs from the pre-formalin response, $p < 0.05$.

3.2 Histology Results of LFP Recording in the PL

Brain slices were stained to observe the location of the electrode tip. Animals with electrode tip outside the target area were excluded from analyses. Representative brain slices (Figure 3.3) and collective electrode tip placement (Figure 3.4) were presented.

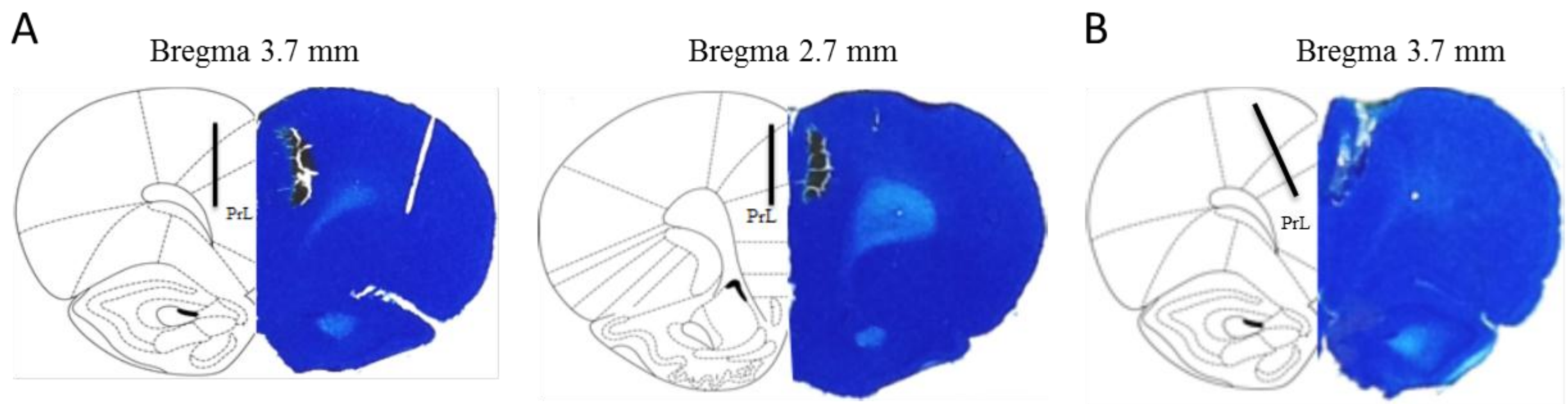

Figure 3.3. Representative brain slices showing the electrode placement.

A: Electrode placement on different coronal slices (electrode straight down in anesthetized animal). B: Electrode placement in freely moving animal when inserted at 20^{o} angle.

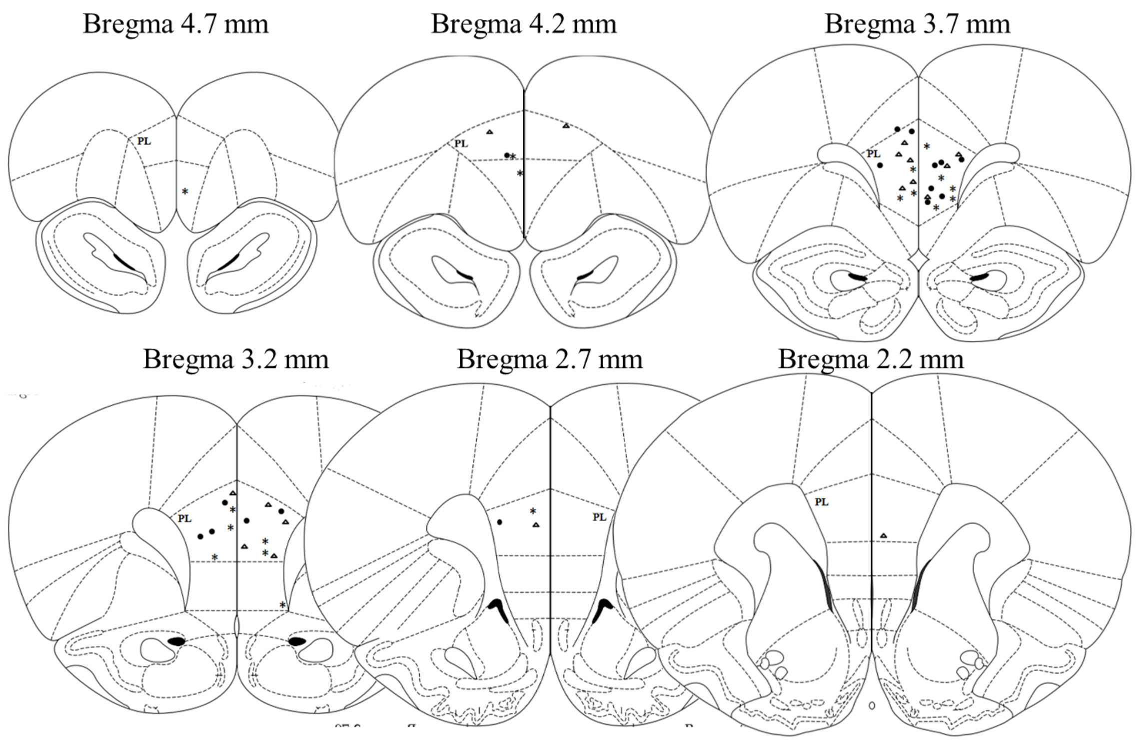

Figure 3.4. Schematic representation of the localization of the electrodes' tips in the PL for each group on different coronal slices anterior to the bregma (modified from Paxinos & Waston, 1998).

Slice at 3.2 mm anterior to the bregma is where PL starts; any slices rostral to this slice are not shown here. *: SN stimulation group of anesthetized animals; ●: natural noxious stimuli group of anesthetized animal; ▲: SN stimulation group of freely moving animals.

3.3 The LFP Responses of the PL in Anesthetized Animal

3.3.1 Certain SN Stimulations Inhibited the LFP Activities in the PL Bilaterally

The LFP was recorded in the PL of the mPFC in response to electrical stimulations of L5 SN at different intensities (10 Hz, 1 ms, 5 s from 0.1v to 5v). Each rat had LFP recording in both left and right PL. A total of 14 rats were included in this experiment, but only 8 out of 14 contralateral recordings and 7 out of 14 ipsilateral recordings were included in analyses due to the exclusions. Based on the overall power of LFP in the target area, the SN electrical stimulation showed a significant inhibitory effect on the LFP starting at 1v on the contralateral side except for 5v (Figure 3.5 A). In contrast to the inhibitory effect of most stimulations, 0.1v stimulation significantly increased the LFP in the contralateral PL (Figure 3.5 A). On the ipsilateral side, the inhibition started at higher voltages (3v) (Figure 3.5 C) as compared with contralateral side. For off-target areas, the inhibition was less pronounced and only appeared at post-stimulation period (Figure 3.5 B & D). It means that this inhibitory effect of SN electrical stimulation is specific to PL to some extent.

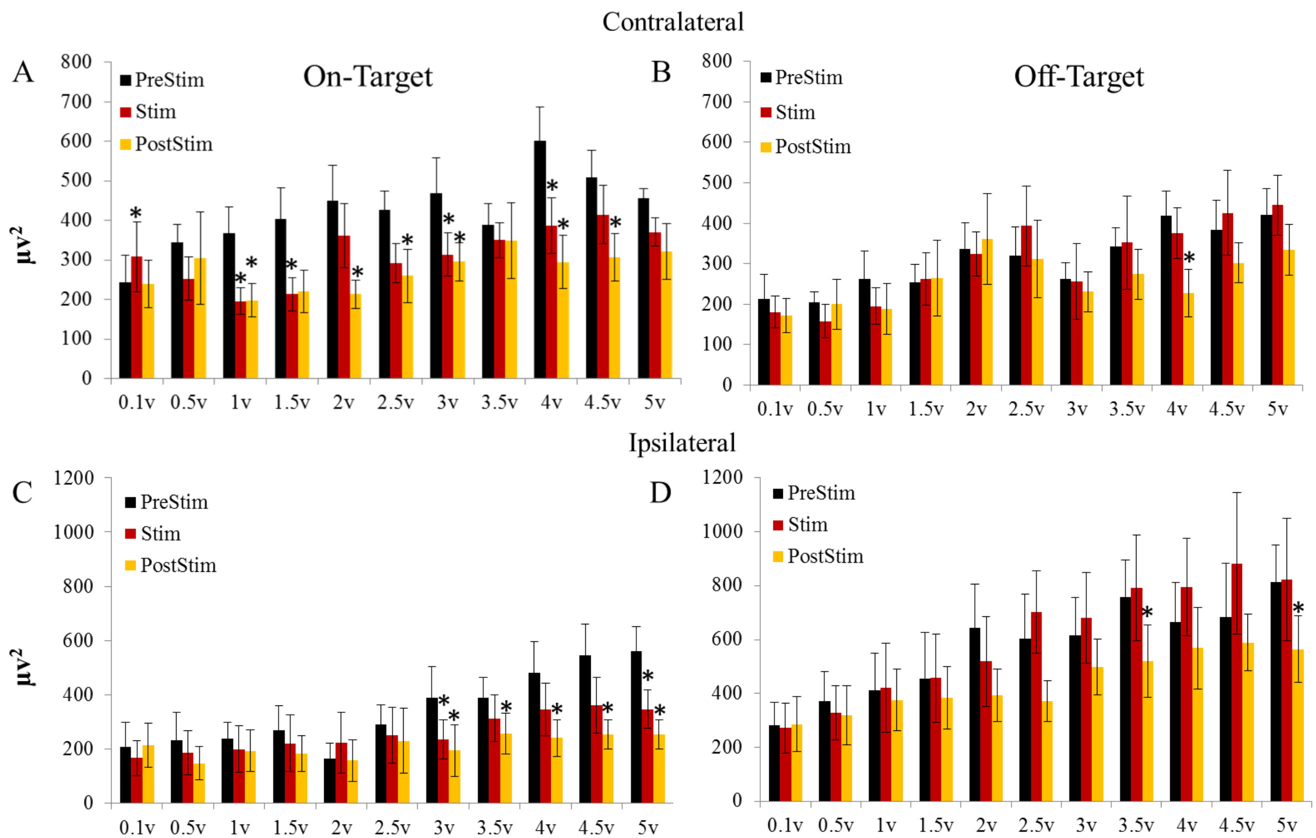

Figure 3.5. Overall LFP responses in the PL to SN stimulations under anesthesia.

PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. A & B: results for contralateral side (On-Target: n = 8; Off-Target: n = 6); C & D: results for ipsilateral side (On-Target: n = 7; Off-Target: n = 7). *: response significantly differs from the pre-stimulation period, $p < 0.05$.

In further frequency band analysis of the contralateral side, delta band did not show significant inhibition; the inhibition for theta band was mainly around lower-intensity stimulations (0.5v-2v), while inhibition for alpha and beta band was around high intensity stimulations; inhibition in Gamma was not as significant as other frequency bands (Figure 3.6). For ipsilateral side, all frequency bands showed some significant inhibitions at stimulations higher than or equal to 2.5v (Figure 3.6). The frequency band analysis of off-target area showed overall less significant inhibitory effect compared with target area; see Figure 3.7 for detailed information.

The values of mean ± SE for LFP responses in PL to SN stimulations under anesthesia were provided in Table A.1—Table A.4 in Appendix A.

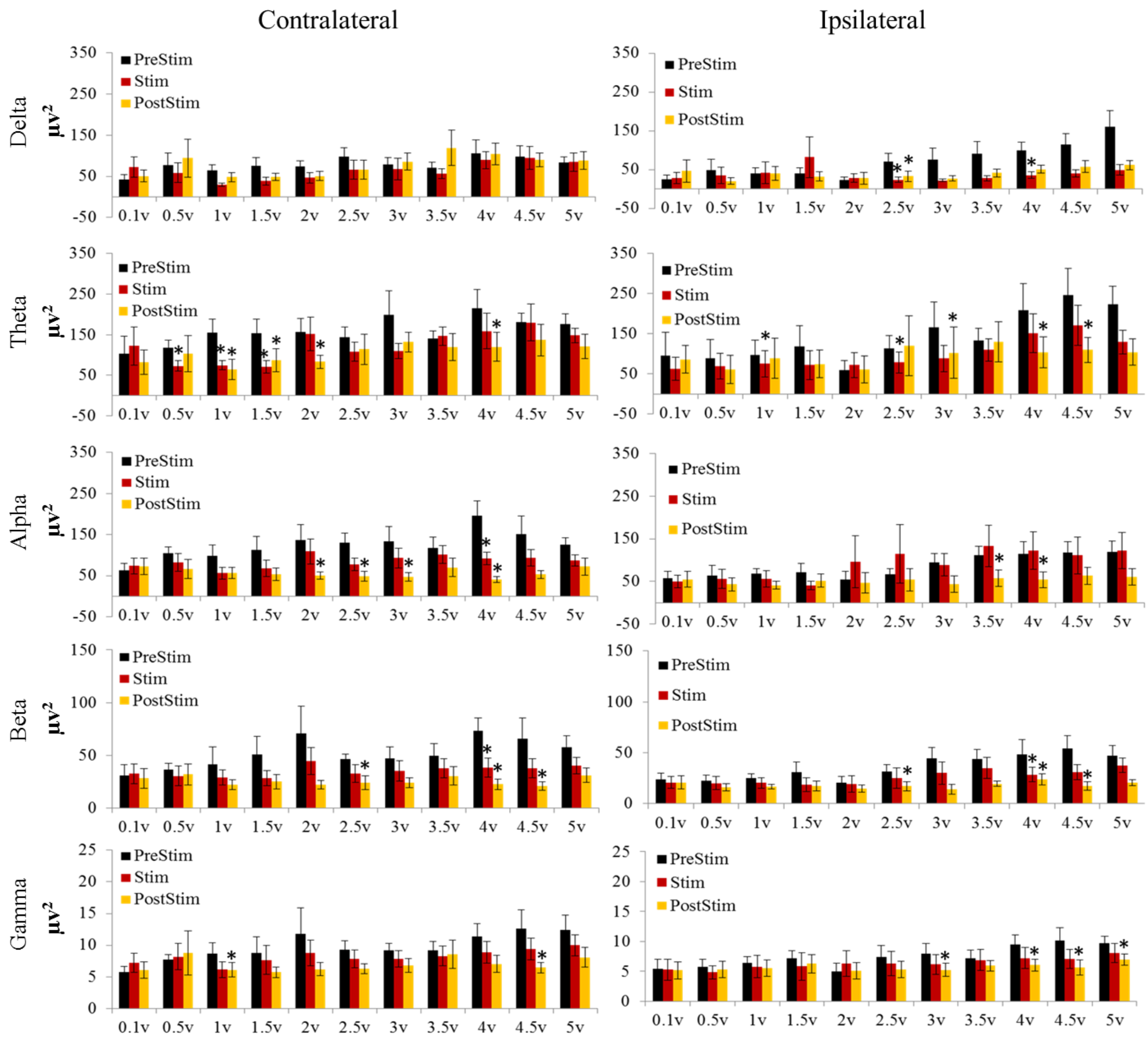

Figure 3.6. LFP responses of different frequency bands in the PL to SN stimulations under anesthesia (On-Target).

Contralateral side: n = 8; ipsilateral side: n = 7. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

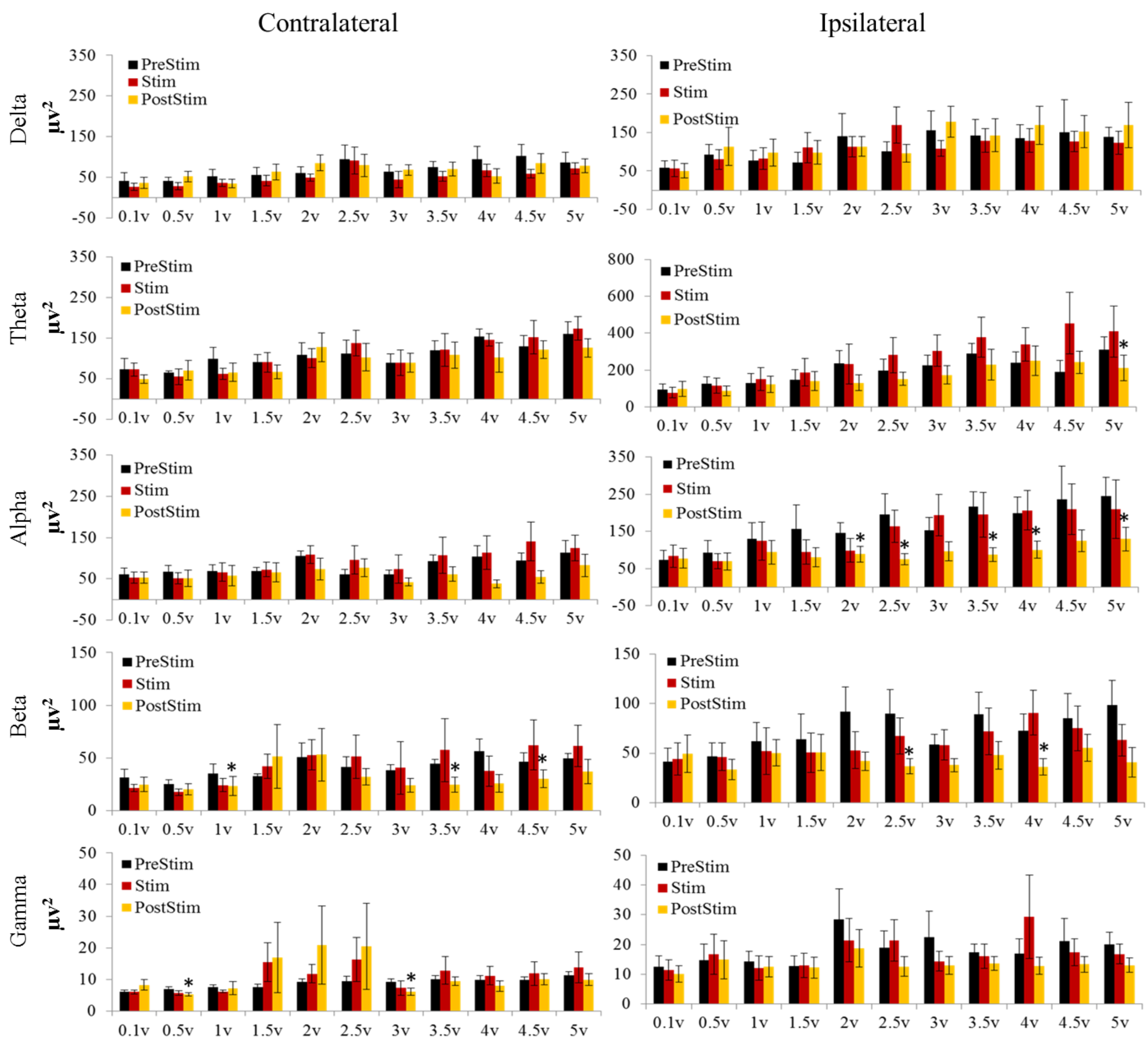

Figure 3.7. LFP responses of different frequency bands in the PL to SN stimulations under anesthesia (Off-Target).

Contralateral side: n = 6; ipsilateral side: n = 7. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

3.3.2. Natural Noxious Stimuli Inhibited LFP Activities in the PL.

The LFP responses in the PL to mechanical stimuli (brush, pressure, and pinch) and formalin injection have also been investigated to further confirm the effect of noxious input on the LFP of the PL.

3.3.2.1. LFP Responses to Mechanical Stimuli

Five seconds before, during and after mechanical stimulation were taken for analysis. The overall power (1 Hz to 100 Hz) of the LFP in both contralateral and ipsilateral PL showed significant inhibition during pinch stimulation of the left hind paw (Figure 3.8). Brush increased the LFP in the contralateral PL although it's not significant. In contrast, brush significantly decreased LFP on the ipsilateral PL. Both contralateral and ipsilateral LFP had the tendency of increased activity during pressure stimulation. In further frequency bands analysis, however, the only significant change observed was the decreased theta band response to brush in the LFP of ipsilateral PL (Figure 3.9). The values of mean ± SE for LFP responses to mechanical stimuli were provided in Table B.1. and Table B.2 of Appendix B.

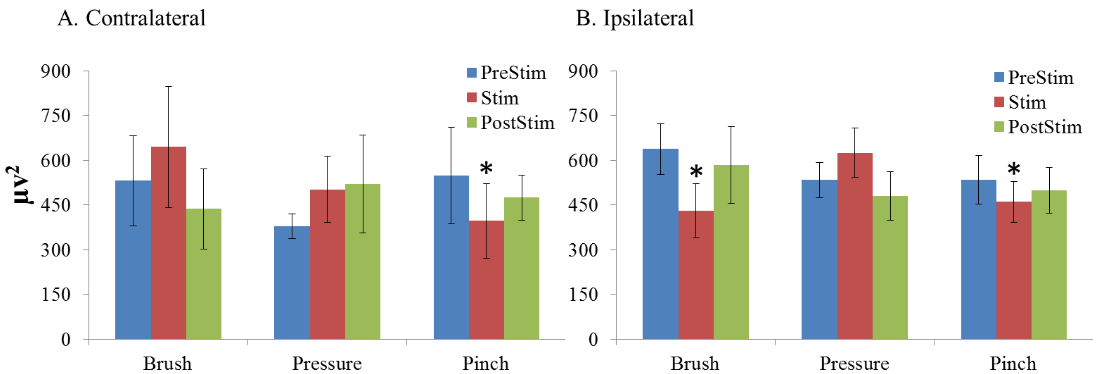

Figure 3.8. Overall LFP responses in the PL to mechanical stimuli under anesthesia. Contralateral side: n = 7; ipsilateral side: n = 8. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

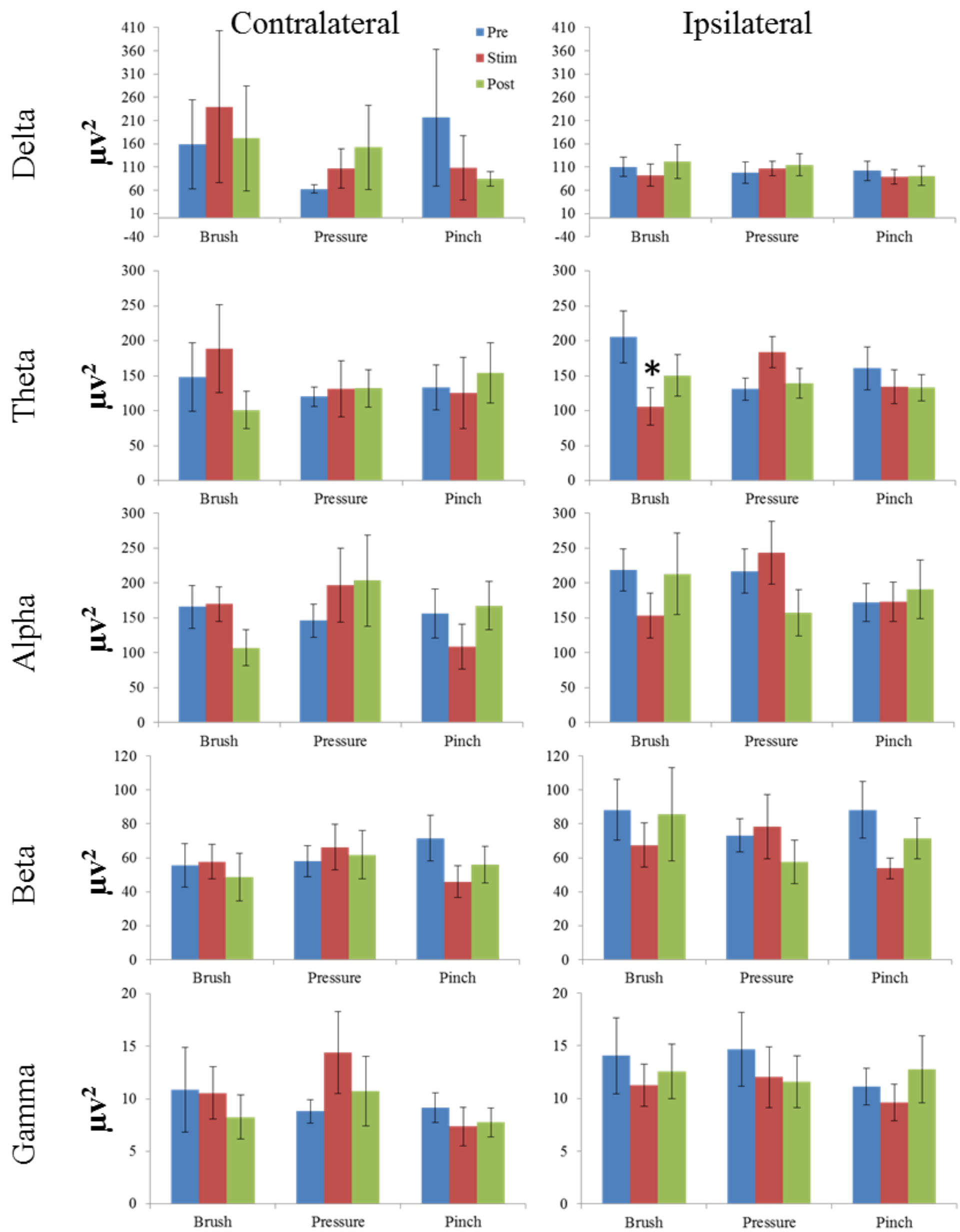

Figure 3.9. LFP responses of different frequency bands in the PL to mechanical stimuli under anesthesia.

Contralateral side: n = 7; ipsilateral side: n = 8. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

3.3.2.2. LFP Responses to Formalin Injection

Five seconds before formalin injection were taken as baseline for the LFP. Five seconds at the beginning of every 5 minutes after injection were taken to serve as post-formalin data points. The overall power of LFP decreased immediately after formalin injection, but is only significant on the ipsilateral side (Figure 3.10). Then LFP increased back to baseline level, and even higher than the baseline at the end of the recording in contralateral PL. In further frequency band analysis, beta and gamma band showed significant increase at later time points on the contralateral side; alpha and beta band showed significant decrease immediately after formalin injection (see Figure 3.11 for more information). The values of mean ± SE for LFP responses in PL to formalin injection were provided in Table C.1 and Table C.2 of Appendix C.

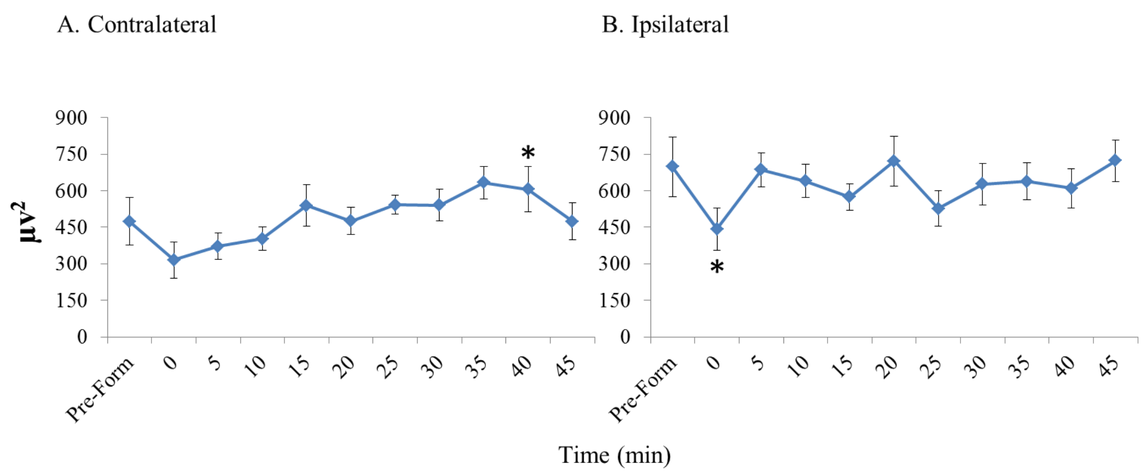

Figure 3.10. Overall LFP responses in the PL to formalin injection under anesthesia. Contralateral side: n = 7; ipsilateral side: n = 8. Pre-Form: Pre-formalin. *: response significantly differs from the pre-formalin period, $p < 0.05$.

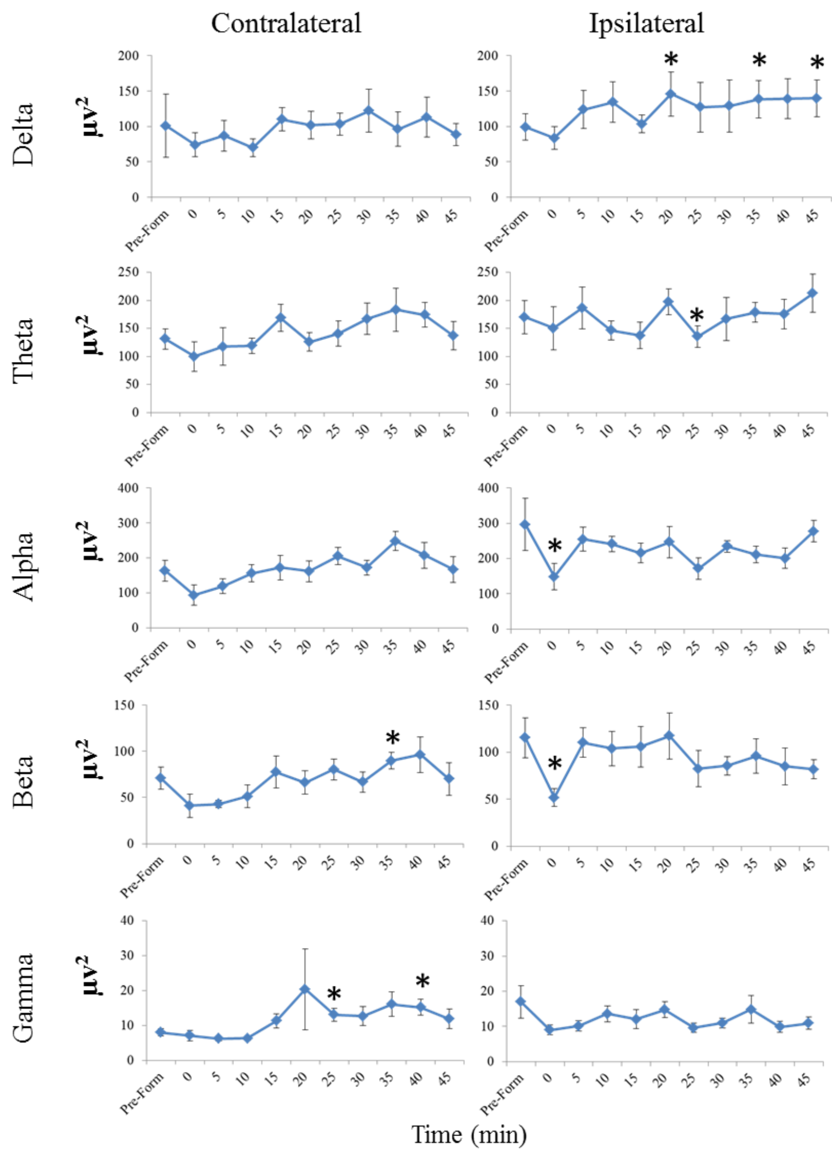

Figure 3.11. LFP responses of different frequency bands in the PL to formalin injection under anesthesia.

Pre-Form: pre-formalin. Contralateral side: n = 7; ipsilateral side: n = 8. Pre-Form: Pre-formalin. *: response significantly differs from the pre-formalin period, $p < 0.05$.

3.4 The LFP Recording in Freely Moving Animal

3.4.1 Mechanical Paw Withdraw Threshold (MPWT) Testing

MPWT was measured to determine if cuff electrode implantation changed mechanical threshold. The Overall results showed no difference in MPWT for each paw before and after implantation; and there was no significant difference between the left and right paw (Figure 3.12).

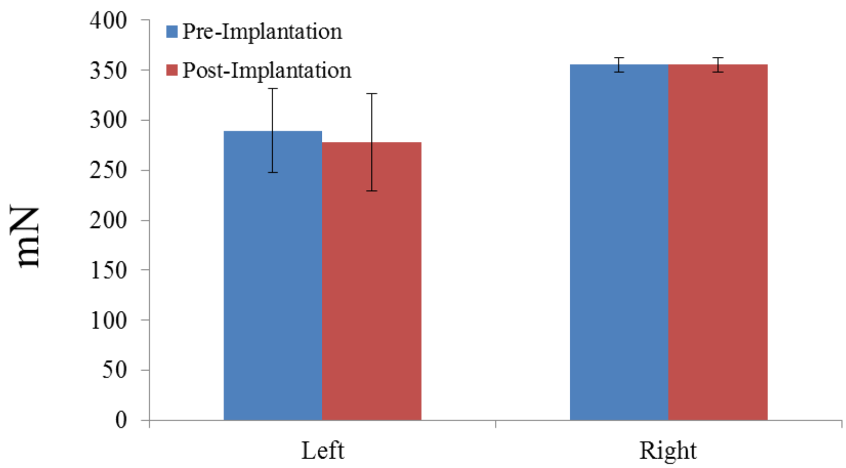

Figure 3.12. The mechanical withdraw pain threshold before and after cuff electrode implantation.

3.4.2. LFP Responses to SN Stimulation

A total of 9 rats were included in this experiment. Each rat had both contralateral and ipsilateral PL recording. So, 9 contralateral and 9 ipsialteral recordings were included in analyses. The recording in freely moving animal had some limitations. The sensory input was produced by electrical stimulation of L5 SN which not only has sensory component, but also motor component. The motor nerve can be activated at low-voltage stimulations based on the observations in this experiment that animals started involuntary shaking of their hind limb and paw between 0.1v and 1.5v (Table 3.1). This involuntary shaking became intense as the voltage increased, and elicited voluntary movement of the animal. This combination of involuntary shaking and voluntary movement resulted in artifact-like signals in the recording (Figure 3.13 A), therefore, recordings in freely moving animal were analyzed in two different ways. Seven different time segments were taken into analysis for each stimulation: 5s before and during stimulation, 5s at the beginning of every 1 minute after stimulation for 5 min. In the first analysis, all data points were included; in the second analysis, data-points with artifact-like signals were excluded from analysis.

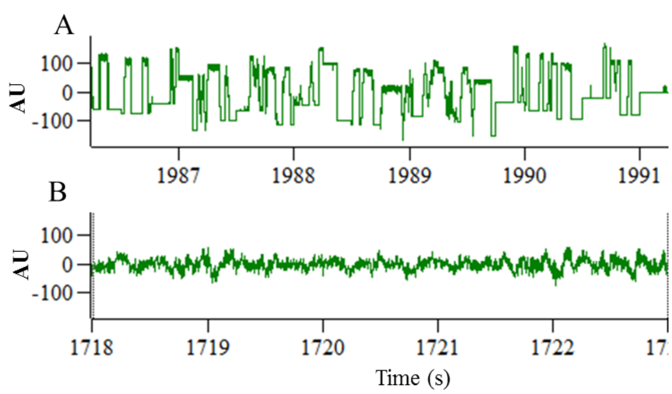

Figure 3.13. Examples of the LFP recording in freely moving animal.

AU: arbitrary unit. A: Recording during stimulation with artifact-like signals. B: Recording without artifact-like signals.

3.4.2.1. Analyses with All Data Points Included

In the first analysis, all the time segments were included in analysis. The overall power drastically increased during stimulation for both contralateral and ipsilateral PL at most stimulations (Figure 3.14). The lack of significance of the effect of 4 v-stimulation on contralateral PL (n = 3) and 5 v-stimulation on ipsilateral PL (n = 2) was due to the small sample size (Figure 3.14 B), because not every animal went through all the stimulations from 0.1v to 5v. Some of the rats were more sensitive to the stimulations than others, they showed involuntary shaking and vocalization at lower voltage stimulation. The stimulation was stopped at one or two more stimulations after the rat manifested vocalization, since the animal was extremely stressed. If the animal didn't show any vocalization, then the stimulation continued to increase to the highest voltage (5v) that the wireless stimulator can deliver. After the drastic increase of power during stimulation, power went down but is still higher than baseline at various post-stimulation time points. Further frequency band analysis showed similar trend (Figure 3.15 & Figure 3.16)

Table D.1 and Table D.2 in Appendix D provided detailed information about the sample size for each stimulation and the values of mean ± SE for LFP responses in PL to SN stimulations.

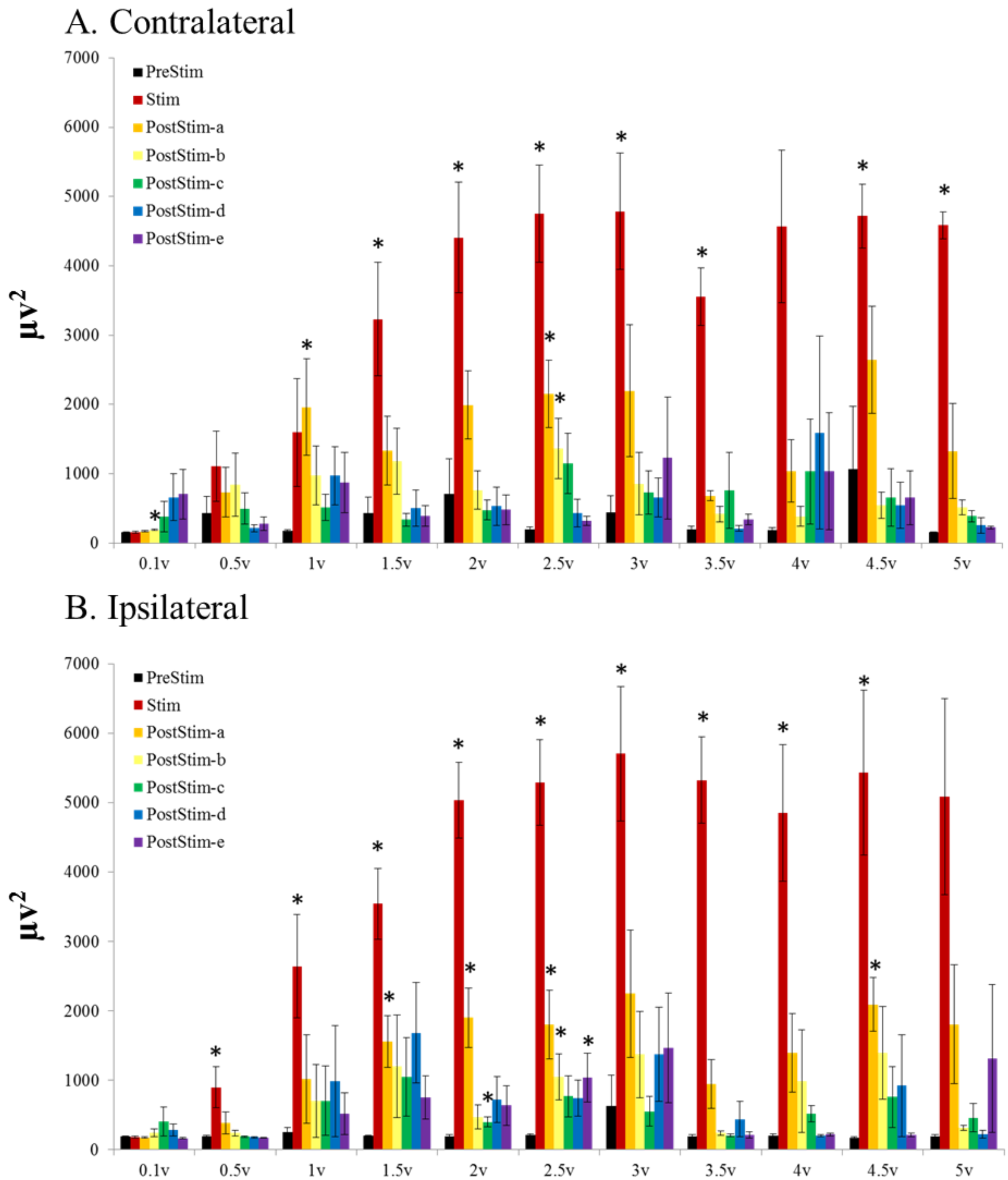

Figure 3.14. Overall LFP responses in the PL to SN stimulations in freely moving animal (with all data points included).

N = 9 for each side. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

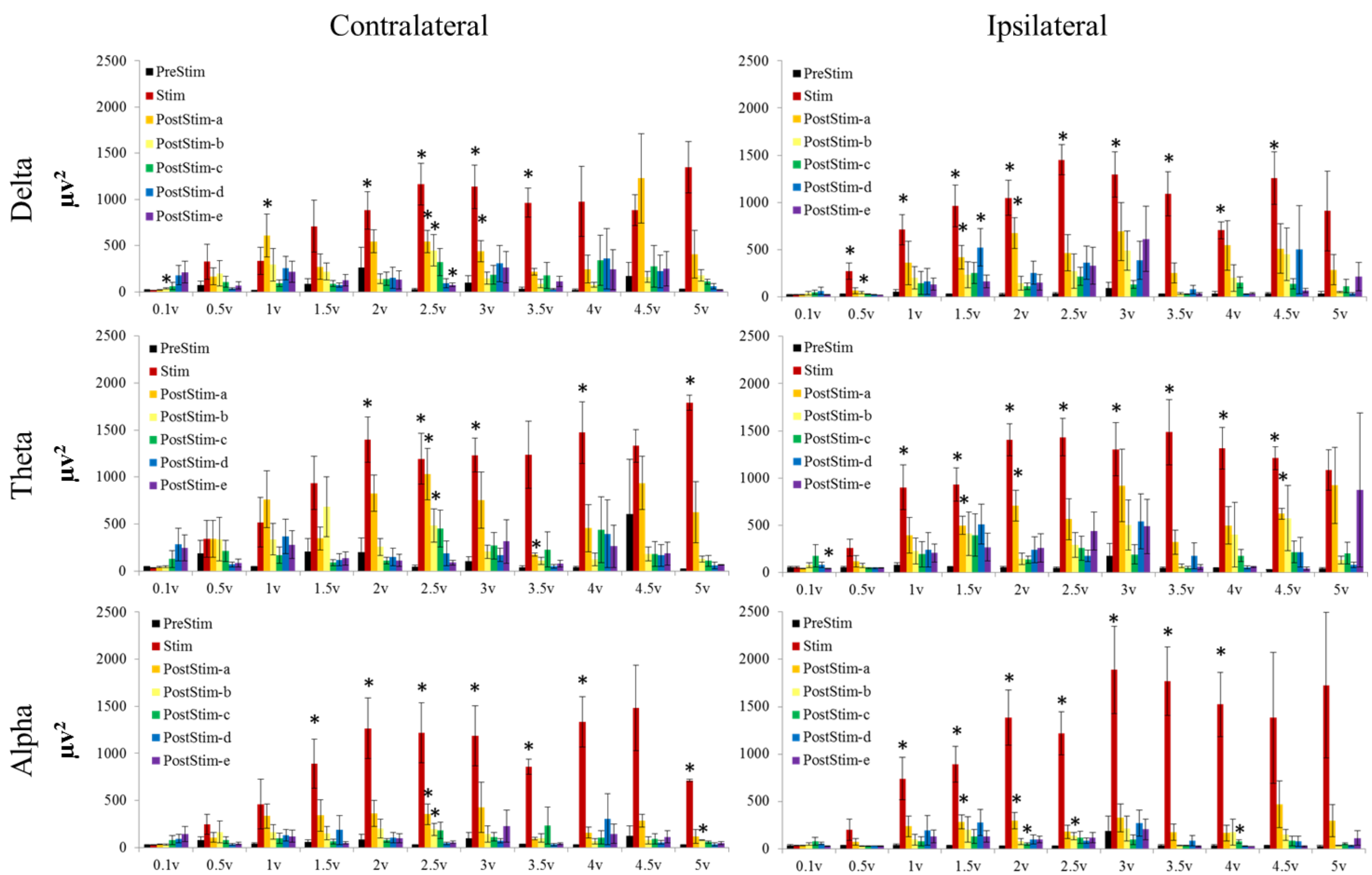

Figure 3.15. LFP responses of delta, theta and alpha band to SN stimulations in freely moving animal (with all data points included). N = 9 for each side. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

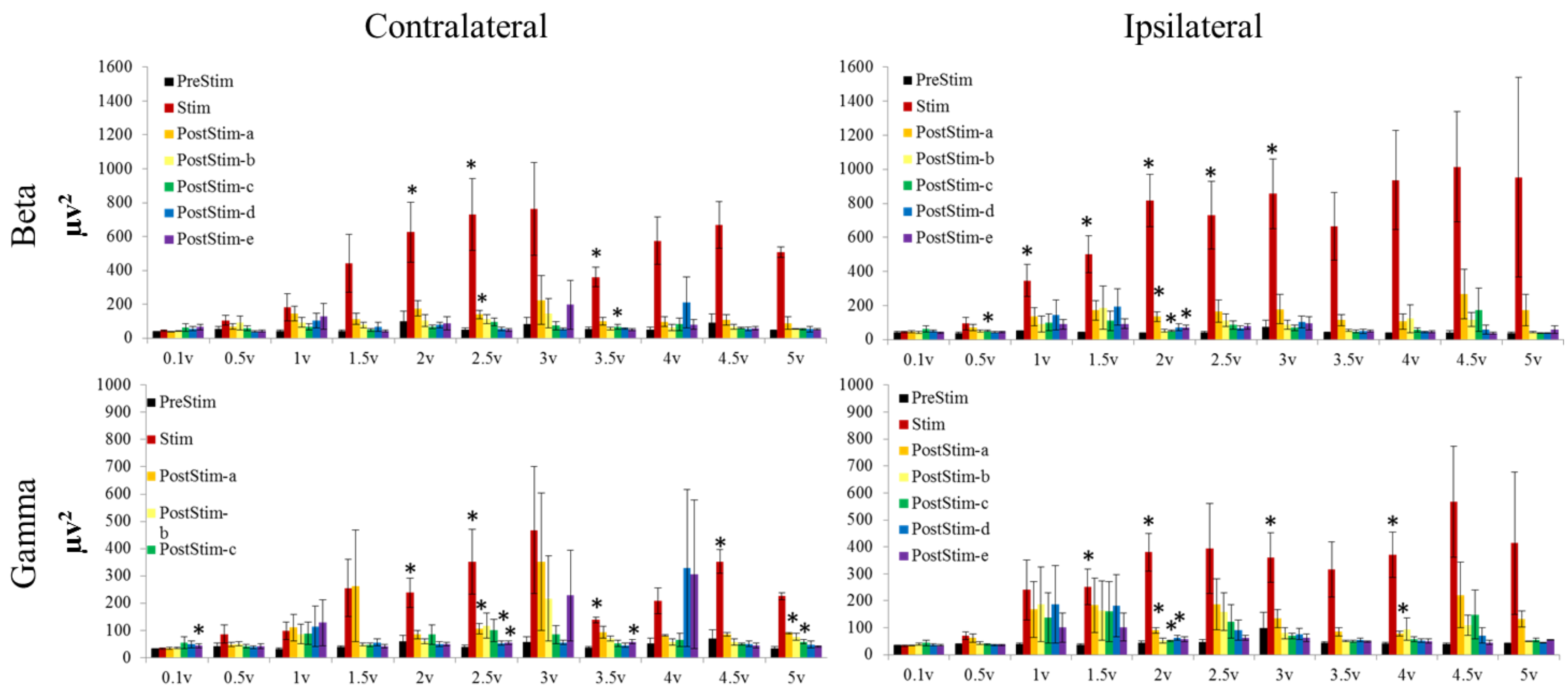

Figure 3.16. LFP responses of beta and gamma band to SN stimulations in freely moving animal (with all data points included).

N = 9 for each side. PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

3.4.2.2. Analyses with Some Data Points Excluded Following Justification

Because raw traces could be contaminated by the stimulus artifact during electrical stimulation, in further analyses with manual verification, data points with artifact-like signals were taken out from the analysis. In addition, all data during stimulation and the first time point after stimulation were taken out for all rats, because those two time segments had most animal movement. Some other data points were taken out if obvious artifact-like signals were observed during corresponding time segment after carefully examining the raw recording trace of LFP. The overall power after stimulations still seems to be higher than baseline at most post-stimulation time points (Figure 3.17). Due to the big variation, significance only showed at few time points. Further frequency band analysis showed similar trend and higher frequency bands showed significance at multiple post-stimulation time points (Figure 3.18 & Figure 3.19).

Table D.3 and Table D.4 in Appendix D provided detailed information about the sample size for each condition; Table D. 5and Table D.6 provided the values of mean ± SE for LFP responses in PL to SN stimulations.

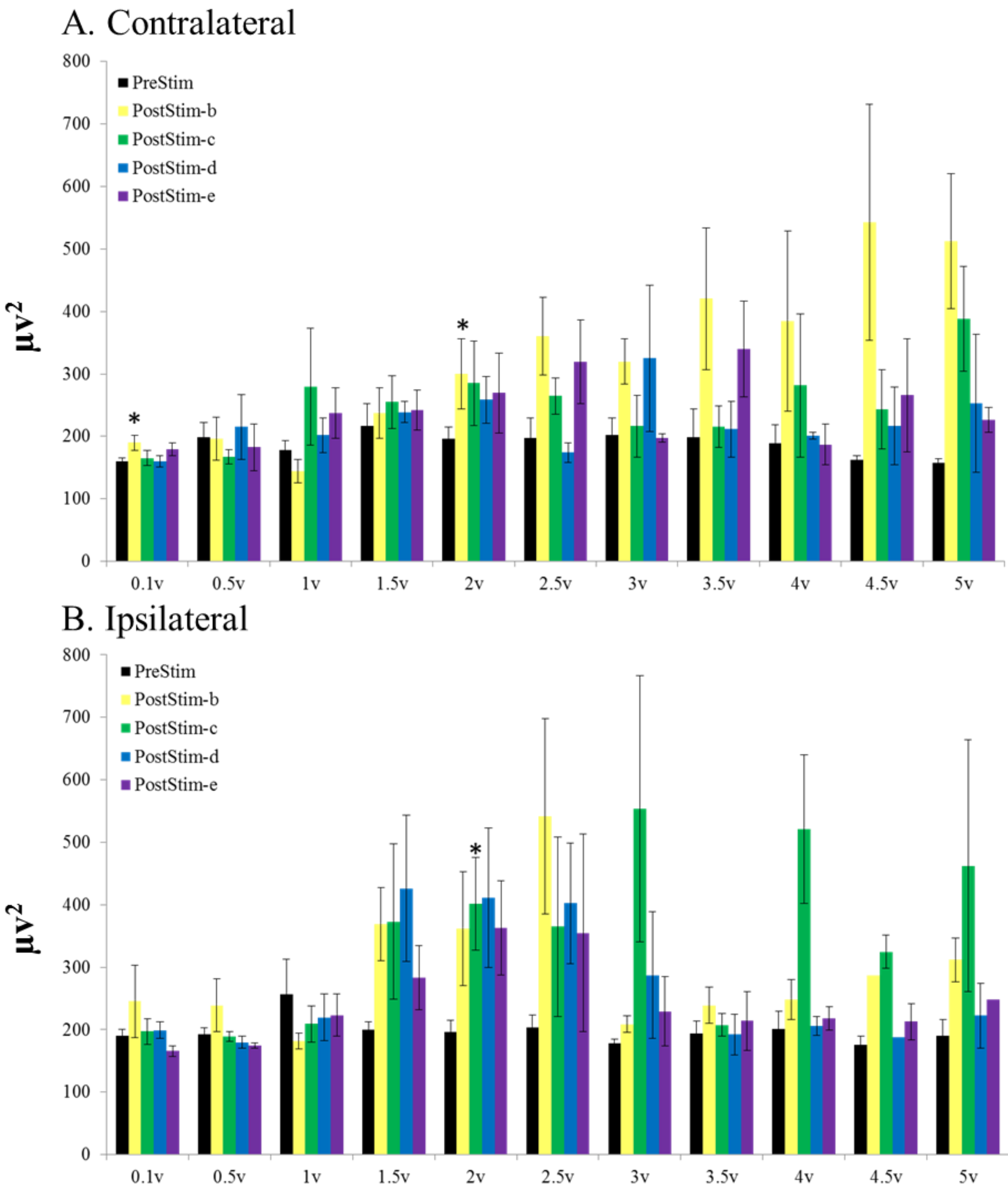

Figure 3.17. Overall LFP responses in the PL to SN stimulations in freely moving animal (following justification).

PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

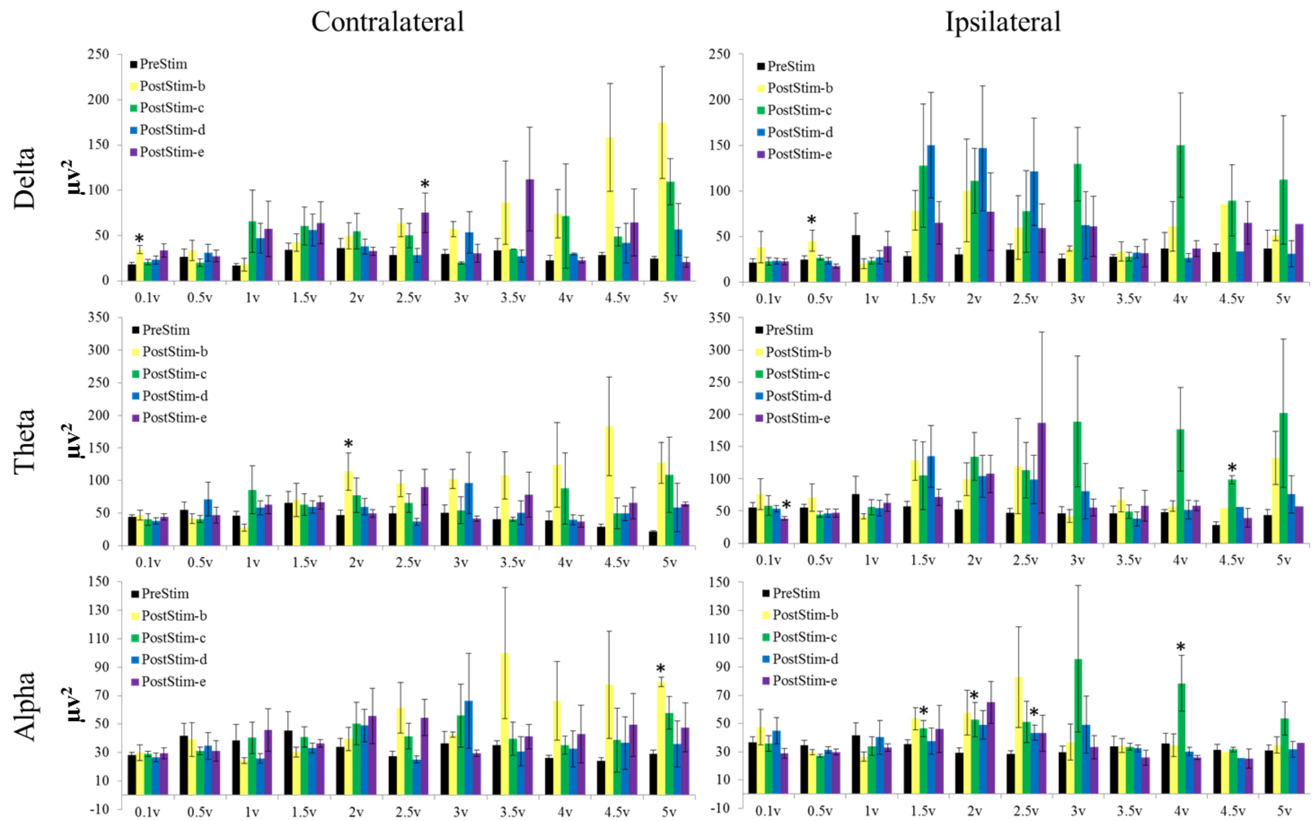

Figure 3.18. LFP responses of delta, theta and alpha band to SN stimulations in freely moving animal (following justification). PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: response significantly differs from the pre-stimulation period, $p < 0.05$.

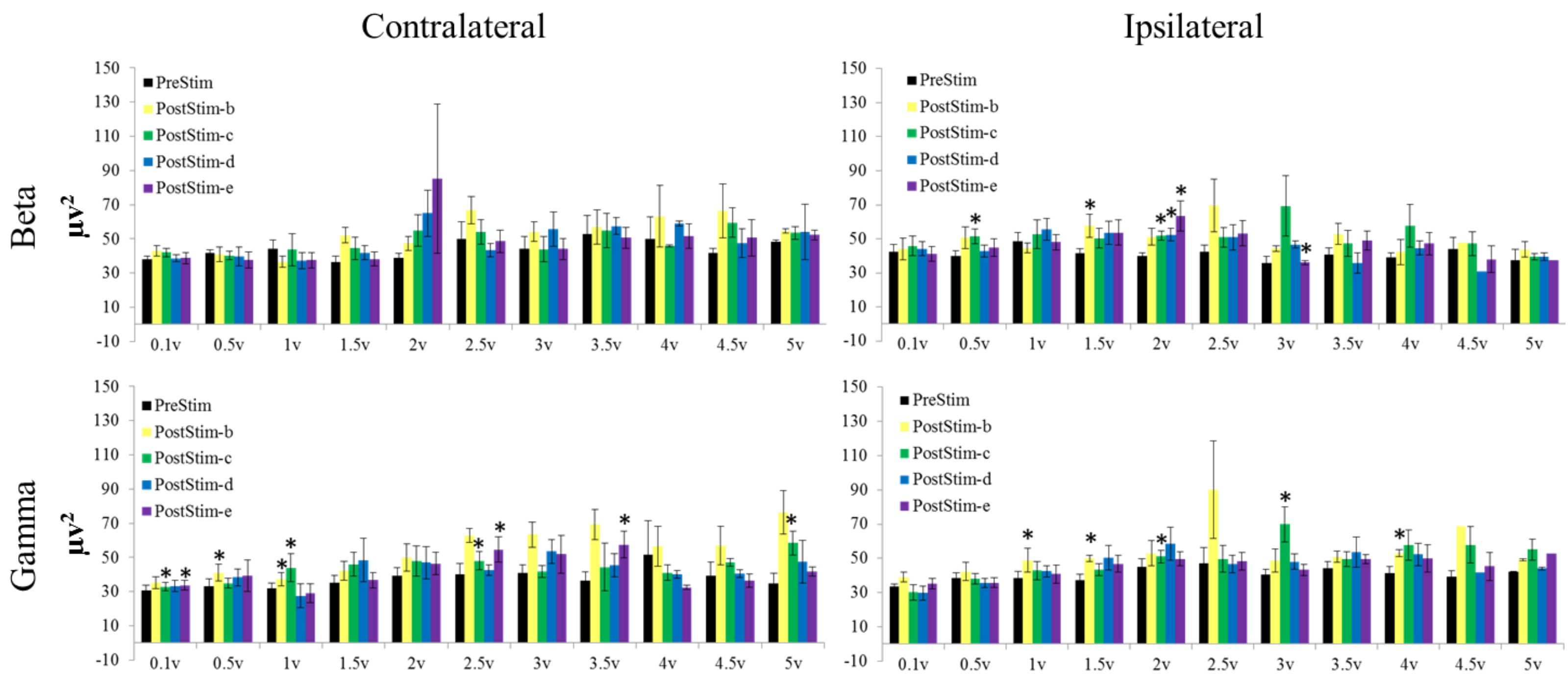

Figure 3.19. LFP responses of beta and gamma band to SN stimulations in freely moving animal (following justification). PreStim: Pre-stimulation; Stim: Stimulation; PostStim: Post-stimulation. *: responses significantly differ from the pre-stimulation period, $p < 0.05$.

3.4.2.3. Observed Behaviors During Stimulation.

Behavior changes accompanied with SN stimulation were noticed during the LFP recording. The onset of involuntary shaking and vocalization was summarized in Table 1.

Table 3.1. Observed behaviors to SN stimulation in freely moving animal.

Rat ID	Start of shaking 1st_stim (v)	Start of shaking 2nd_stim (v)	Start of vocalization 1st_stim (v)	Start of vocalization 2nd_stim (v)
RT011314	1.5	1.5	3.5	3
RT011514	1	1.5		
RT012314A	1.5	0.5	4.5	1
RT012314B	0.5	0.5	2	1.5
RT013014A	1	1	3.5	2
RT013014B	0.5	0.5	1.5	1
RT020314A	0.5	0.5	3.5	3.5
RT020314B	1	1	2.5	1.5
RT020514	1	1	2	1
Mean	0.944	0.889	2.875	1.813
SE	0.130	0.139	0.363	0.340

Note: 1^{st}_stim: 1^{st} set of stimulations; 2^{nd}_stim: 2^{nd} set of stimulations. Since each rat had both contralateral and ipsilateral PL recording, two sets of SN stimulations were applied to each rat.

3.4.3. LFP Responses to Formalin Injection

The effect of formalin injection on the LFP in PL was analyzed to further confirm the effect of nociceptive input. Formalin was injected at the end of SN electrical stimulation. Because no differences in the LFP have been observed between contralateral and ipsilateral PL (Figure 3.20 A & B), values for all rats were grouped to increase the sample size (n = 6). Two baselines were taken. Baseline 1 was before any manipulation, baseline 2 was after electrical stimulation but before formalin injection. No significant difference was observed between those two baselines. There was a trend of increased activity after injection, although it’s not significant (Figure 3.20 C). In further frequency band analysis, alpha and gamma band showed significance at later time point (see Figure 3.21 for detailed information). Table E.1 in Appendix E provided values of mean ± SE.

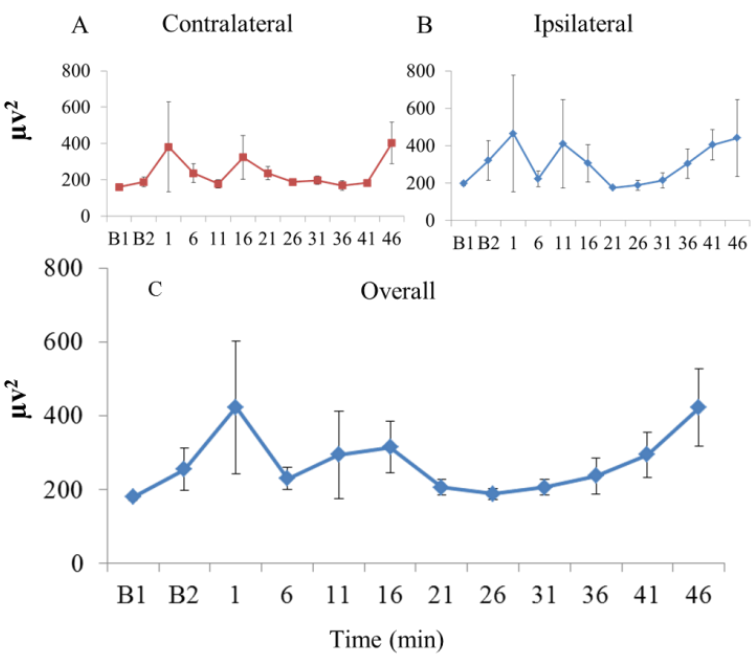

Figure 3.20. Overall LFP responses to formalin injection in freely moving animal. B1: baseline 1; B2: baseline 2. A & B: LFP responses for contralateral and ipsilateral side respectively. C: Combined responses of contralateral and ipsialteral side. *: response significantly differs from the baseline 1, $p < 0.05$.

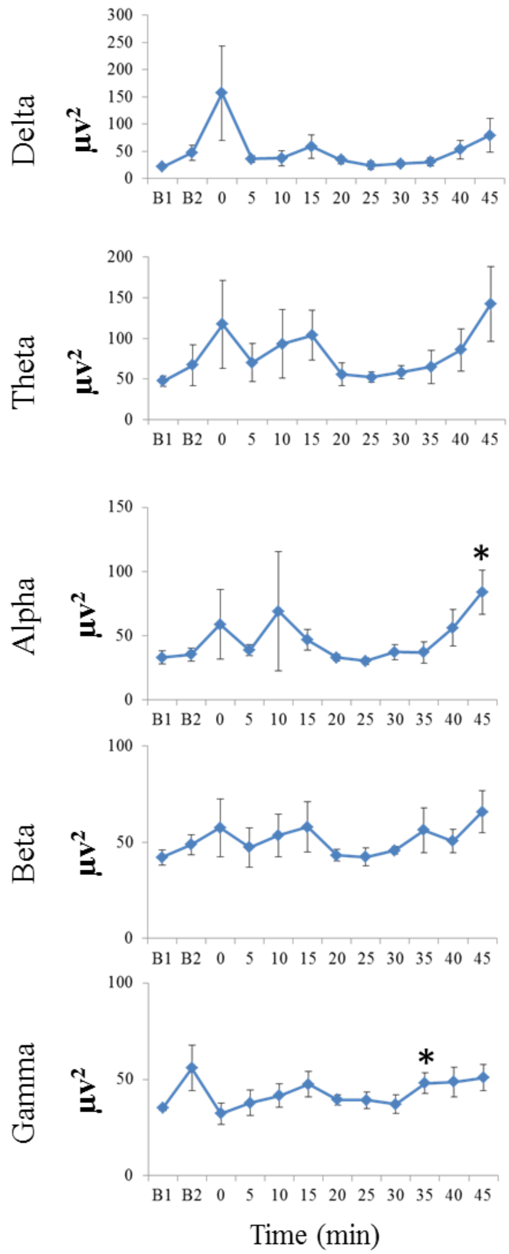

Figure 3.21. LFP responses of different frequency bands to formalin injection in freely moving animal.

B1: baseline 1; B2: baseline 2. *: response significantly differs from the baseline, the pre-formalin period, $p < 0.05$.

Chapter 4

Discussion

This study investigated the effect of peripheral L5 spinal nerve (SN) stimulations on the LFP of the prelimbic (PL) area in the mPFC. It was found that in anesthetized animal, electrical stimulation of L5 SN inhibited the LFP bilaterally in the PL of the mPFC. Contralateral PL was more sensitive to this inhibition caused by SN stimulation (starting at 1v) than ipsilateral PL (starting at 3v) (Figure 3.5 A & C). The DH response caused by L5 SN stimulation at 1v or higher was not statistically different from the response in phase I of formalin injection. It can be speculated that SN stimulation at 1v or higher may result in nociception that is comparable to formalin injection, and resulted in the deactivation of the PL. This result is in line with the finding of Ji and Neugebauer (2011) where the kaolin/carrageenan-induced arthritis inhibited single cell activities in the mPFC. It is interesting that 0.1v stimulation significantly increased the LFP in the contralateral PL (Figure 3.5 A), but had the tendency to decrease the LFP in the ipsilateral PL (Figure 3.5 C). The 0.1v stimulation was too weak to activate any nociceptive fibers, but it might activate some big fibers for innocuous sensation. These observations are in concordance with the LFP responses of PL to mechanical stimulations where brush significantly decreased the LFP in ipsilateral PL (Figure 3.8 A), but had the tendency to increase the LFP in contralateral PL (Figure 3.8 B). However, pinch inhibited LFP for both contralateral and ipsilateral PL (Figure 3.8 A & B). Similarly, the LFP in both contralateral and ipsilateral PL decreased immediately after the formalin injection with significance on the ipsilateral side (Figure 3.10 B). The decrease in LFP caused by formalin injection didn’t appear at a later stage. The absence of decreased LFP at later stage might be explained by the lack of phase II DH response of formalin injection. However, it cannot rule out the possibility that the DH recording after formalin injection was too short (20 min) to show the phase II response, although phase II response started between 15min -20min in other electrophysiological studies (Dickenson & Sullivan, 1987; You, Cao, Yuan, & Arendt-Nielsen, 2006). Taken together, electrical stimulation of L5 SN (at certain levels), and mechanical and chemical noxious stimulations decreased the LFP in the PL of the mPFC. This inhibition was bilateral but with different pattern.

However, in freely moving animals, such inhibition was not observed. The power of LFP increased drastically during and immediately after SN electrical stimulation (Figure 3.14). This increase could be contaminated by the artifact caused by the movement or stimulus artifact, because movement was an inseparable part of the stimulation when it’s became high enough to activate motor fiber component in L5 spinal nerve. Whether these increases were attributable to the activation of sensory fibers in L5 spinal nerve remains to be unsolved and needs further investigation. After carefully removing data points with obvious artifact-like signal (Figure 3.13), the rest data points still did not show inhibition by the SN stimulation. Instead, it showed slight increasing trend of activity after stimulation (Figure 3.17). Similarly, the LFP after formalin injection showed biphasic increase pattern, but it was not significant (Figure 3.20). Overall, in freely moving animal, the SN electrical stimulation and formalin injection has the tendency to increase the LFP in the PL.

The inhibitory effect by SN stimulation and natural noxious stimulation that existed in anesthetized animal was absent in the freely moving animal. The reason for such discrepancy is likely to be due to the additional cognitive and emotional activities going on in awake state. This sudden involuntary muscle contraction caused by SN electrical stimulation surprised animals and might have scared them and created stress. It has been shown that mPFC was involved in the regulation and expressions of fear responses (Etkin, Egner, & Kalisch, 2011). And mPFC has been proven to be very sensitive to stress. Firing rate of neurons in mPFC increased in response to restraint-induced stress (Jackson & Moghaddam, 2006); and mild stress was enough to induce morphological changes (Brown et al., 2005). Noxious stimuli and involuntary movement can both be stressors to rats. Acute foot shock to rat can increase extracellular dopamine concentration of medial prefrontal cortex to 203% of baseline levels (Sorg & Kalivas, 1993). Similar increased mPFC activity was observed in chronic back pain patients when they experienced sustained high spontaneous chronic back pain (Baliki et al., 2006). So, nociception-associated emotional activities in mPFC may have masked the effect of noxious input per se. This complex interaction between nociception and its associated emotional and cognitive changes remains to be explored.

Finally, several evidences in current study imply that SN stimulation at certain intensities is highly likely to produce nociception. First, the DH responses induced by 1v or higher did not significantly differ from the DH responses during phase I of formalin injection. The amplitude of response induced by 3.5v (16.44 ± 3.44 spikes/s), 4v (18.71± 4 spikes/s), 4.5v (19.95 ± 4.28 spikes/s) and 5v (20.35 ± 4.35 spikes/s) were comparable to that induced during phase I (17.03 ± 6.72 spikes/s) of formalin injection (Figure 3.1 B & Figure 3.2). Second, LFP responses of PL to SN stimulation and natural nociceptive inputs were similar. In anesthetized animal, the decreased LFP of the PL by SN stimulations was also observed in LFP responses to chemical (formalin injection) and mechanical (pinch) noxious stimuli. However, in freely moving animal, neither SN stimulations nor formalin injection resulted in inhibition of LFP in PL. Third, animals displayed pain-like behaviors to SN stimulation. As the stimulation intensity increased, animal started looking up, a sign of searching exit for escape. Eventually, animal vocalized at average 3v stimulation and showed great distress. One of them even tried to jump out of the cage. But other signs, such as flinching and licking the paw which were normally present in formalin test, were not observed. The lack of those behaviors might be due to the interference of the involuntary muscle contraction caused by the SN stimulation. On the other hand, intense electrical stimulation can activate a mixed group of fibers in a non-differential fashion; and this nonselective activation can result in unusual sensations (Le Bars, Gozariu, & Cadden, 2001). In contrast, natural nociceptive stimulus activates specific fibers and nociceptors. It is not surprising that the quality of the sensation caused by nerve stimulation and formalin injection would be very different. Different sensations can result in different behavior phenotype. Taken together, it is highly possible that certain intensities of L5 SN stimulation can result in pain. However, more tests are needed in the future to further verify this cuff electrode stimulation model.

In conclusion, electrical stimulation of L5 SN at certain intensities inhibited the LFP in PL in anesthetized animal. Similar inhibitions were observed in mechanical and chemical noxious stimulation. However, the inhibition observed in anesthetized animal disappeared in freely moving animal. Given the role of mPFC in cognition and emotion (Etkin et al., 2011; Euston, Gruber, & McNaughton, 2012; Ridderinkhof, Nieuwenhuis, & Braver, 2007), it is important to study how nociception influences the mPFC which will provide an insight to the pain associated cognitive deficits and psychological disorders. This study provided the LFP response profile of mPFC to SN stimulation, mechanical and chemical noxious stimulus. These findings can serve as the foundation for future investigation of the effect of nociception on mPFC, such as which particular neurons are involved in this inhibitory effect of nociception on mPFC. The cuff electrode L5 SN stimulation model employed in this study offered a way to deliver quantifiable and reproducible afferent signals. It is highly likely that these SN stimulations at certain intensities are able to produce nociceptive signals; however, more tests are still needed to further verify this model.

Appendix A

Results in Table: the Effect of SN Stimulations on the LFP of PL under Anesthesia

Table A.1. The effect of SN stimulations on the LFP of contralateral PL under anesthesia.

		0.1v	0.5v	1v	1.5v	2v	2.5v	3v	3.5v	4v	4.5v	5v
Overall	PreStim	244.27±67.31	343.77±46.22	366.83±67.61	402.82±79.14	449.79±90.38	427.07±46.10	468.54±90.14	387.95±54.61	601.39±86.43	509.50±67.57	455.39±25.48
	Stim	308.22±88.53 (***p=0.041***)	252.39±55.39 (p=0.114)	195.18±33.43 (***p=0.011***)	213.42±42.07 (***p=0.018***)	361.08±81.38 (p=0.198)	292.30±49.57 (p=0.064)	313.57±55.34 (***p=0.033***)	350.12±44.54 (p=0.482)	386.85±70.35 (***p=0.017***)	414.74±74.12 (p=0.147)	370.08±36.00 (p=0.116)
	PostStim	238.86±60.00 (p=0.828)	304.55±117.59 (p=0.739)	197.38±42.08 (***p=0.016***)	219.70±53.85 (p=0.059)	213.35±35.71 (***p=0.017***)	259.21±68.20 (***p=0.017***)	295.48±48.93 (***p=0.037***)	348.09±95.82 (p=0.733)	294.61±67.19 (***p=0.003***)	306.51±60.97 (***p=0.013***)	320.99±71.22 (p=0.131)
Delta	PreStim	42.77±10.76	78.03±28.06	64.33±14.24	76.42±19.07	74.25±13.64	97.41±22.51	79.36±15.59	71.28±13.60	106.62±32.25	97.68±27.19	83.05±14.68
	Stim	72.43±24.44 (p=0.117)	58.30±23.91 (p=0.590)	29.50±4.69 (p=0.065)	38.38±9.26 (p=0.074)	46.73±12.44 (p=0.156)	66.57±22.72 (p=0.205)	67.67±25.70 (p=0.705)	56.37±12.02 (p=0.501)	89.30±20.00 (p=0.596)	94.74±27.26 (p=0.950)	84.54±22.41 (p=0.964)
	PostStim	50.56±14.37 (p=0.480)	94.16±46.88 (p=0.752)	48.28±11.19 (p=0.196)	49.30±8.89 (p=0.237)	50.97±11.64 (p=0.130)	66.25±23.26 (p=0.703)	85.37±20.72 (p=0.846)	119.42±43.24 (p=0.298)	104.79±26.12 (p=0.910)	89.74±16.43 (p=0.778)	88.35±21.38 (p=0.835)
Theta	PreStim	102.30±44.38	117.65±18.22	154.48±33.54	154.23±33.70	156.57±32.67	144.07±24.02	198.60±58.78	140.91±18.84	214.62±46.17	181.46±21.49	176.69±24.99
	Stim	122.45±46.97 (p=0.166)	72.81±13.07 (***p=0.034***)	74.50±11.77 (***p=0.032***)	70.96±15.49 (***p=0.012***)	152.22±41.55 (p=0.927)	108.27±23.37 (p=0.363)	109.63±18.90 (p=0.139)	146.23±22.15 (p=0.833)	158.90±43.62 (p=0.331)	179.46±45.49 (p=0.969)	148.35±18.05 (p=0.354)
	PostStim	82.05±30.57 (p=0.278)	103.13±44.53 (p=0.700)	64.34±24.69 (***p=0.004***)	86.25±28.48 (***p=0.032***)	83.52±16.21 (***p=0.035***)	113.70±36.71 (p=0.424)	131.56±24.11 (p=0.155)	119.77±32.89 (p=0.540)	119.85±35.73 (***p=0.012***)	136.61±38.43 (p=0.108)	121.33±30.35 (p=0.160)
Alpha	PreStim	62.68±16.66	104.16±16.46	98.31±26.87	112.91±33.20	136.20±38.69	129.87±23.29	134.37±34.67	116.86±27.50	195.76±36.60	151.98±44.00	125.60±16.53
	Stim	73.72±19.09 (p=0.101)	82.73±21.20 (p=0.393)	56.32±14.08 (p=0.164)	68.02±19.85 (p=0.240)	108.98±30.74 (p=0.383)	77.12±15.09 (p=0.109)	93.36±24.13 (p=0.201)	101.50±21.00 (p=0.523)	91.56±15.14 (***p=0.019***)	93.66±20.27 (p=0.108)	87.05±13.10 (p=0.123)
	PostStim	72.12±19.93 (p=0.419)	66.75±23.24 (p=0.240)	56.73±13.86 (p=0.119)	53.41±15.75 (p=0.168)	50.52±9.12 (***p=0.045***)	49.19±12.32 (***p=0.011***)	47.78±10.39 (***p=0.024***)	69.87±22.57 (p=0.226)	40.48±7.49 (***p=0.004***)	52.96±9.65 (p=0.060)	72.23±20.84 (p=0.155)
Beta	PreStim	30.72±10.62	36.24±6.20	41.09±16.51	50.48±17.23	70.98±25.55	46.45±4.58	47.07±11.07	49.74±11.31	73.05±12.61	65.78±19.31	57.66±10.91
	Stim	32.41±9.45 (p=0.643)	30.40±9.18 (p=0.229)	28.72±7.22 (p=0.373)	28.41±7.17 (p=0.191)	44.37±12.86 (p=0.298)	32.52±8.44 (p=0.195)	35.11±9.74 (p=0.406)	37.73±9.13 (p=0.321)	38.22±8.89 (***p=0.035***)	37.49±8.92 (p=0.151)	40.14±7.73 (p=0.166)
	PostStim	28.07±9.24 (p=0.423)	31.75±9.97 (p=0.541)	21.92±4.62 (p=0.175)	25.01±6.90 (p=0.203)	22.13±3.93 (p=0.087)	23.80±6.53 (***p=0.008***)	23.97±4.92 (p=0.067)	30.45±8.44 (p=0.112)	22.46±4.92 (***p=0.004***)	20.75±3.94 (***p=0.026***)	30.99±7.03 (p=0.066)
Gamma	PreStim	5.80±0.87	7.69±0.85	8.63±1.78	8.79±2.48	11.79±4.11	9.27±1.37	9.14±1.14	9.15±1.47	11.35±2.02	12.61±2.95	12.39±2.40
	Stim	7.21±1.48 (p=0.151)	8.15±2.08 (p=0.783)	6.13±1.24 (p=0.120)	7.65±2.27 (p=0.695)	8.78±2.01 (p=0.462)	7.82±1.37 (p=0.488)	7.80±1.28 (p=0.308)	8.29±1.55 (p=0.590)	8.88±1.70 (p=0.165)	9.39±1.68 (p=0.162)	10.00±1.66 (p=0.317)
	PostStim	6.06±1.34 (p=0.763)	8.76±3.45 (p=0.768)	6.11±1.16 (***p=0.038***)	5.73±0.85 (p=0.216)	6.21±1.05 (p=0.172)	6.27±0.80 (p=0.080)	6.80±1.12 (p=0.085)	8.58±2.23 (p=0.846)	7.03±1.32 (p=0.083)	6.45±0.83 (***p=0.046***)	8.09±1.52 (p=0.156)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table A.2. The effect of SN stimulations on the LFP of ipsilateral PL under anesthesia.

		0.1v	0.5v	1v	1.5v	2v	2.5v	3v	3.5v	4v	4.5v	5v
Overall	PreStim	206.74±90.33	230.48±103.69	237.36±61.63	269.01±89.20	164.19±55.79	291.35±71.39	389.71±114.36	387.39±77.36	480.09±116.56	544.31±114.43	561.21±89.54
	Stim	165.50±63.28 (p=0.265)	185.49±81.72 (p=0.216)	198.57±85.96 (p=0.267)	219.92±105.15 (p=0.436)	221.44±112.30 (p=0.413)	248.89±102.68 (p=0.407)	235.46±72.00 ***(p=0.026)***	312.39±86.38 (p=0.347)	345.55±97.47 (p=0.141)	360.70±101.77 (p=0.175)	346.59±71.23 ***(p=0.023)***
	PostStim	213.01±80.85 (p=0.887)	146.16±61.57 (p=0.103)	192.84±76.00 (p=0.236)	182.61±67.13 (p=0.080)	156.42±76.90 (p=0.844)	229.42±119.29 (p=0.432)	193.43±95.28 ***(p=0.007)***	255.14±74.87 ***(p=0.010)***	239.19±67.52 ***(p=0.016)***	254.32±53.65 ***(p=0.007)***	253.84±53.67 ***(p=0.006)***
Delta	PreStim	25.67±9.68	48.75±28.24	40.69±13.61	40.19±14.15	23.66±7.66	70.14±22.12	76.12±28.65	91.76±31.18	99.09±21.99	115.32±27.50	161.14±40.59
	Stim	27.62±14.44 (p=0.752)	35.08±21.05 (p=0.157)	41.76±28.12 (p=0.946)	82.18±52.51 (p=0.333)	27.91±10.79 (p=0.310)	24.09±6.34 ***(p=0.030)***	21.90±3.54 (p=0.084)	27.58±7.30 (p=0.114)	35.86±8.99 ***(p=0.041)***	39.99±9.09 (p=0.056)	49.28±13.20 (p=0.055)
	PostStim	46.20±28.28 (p=0.332)	20.58±8.39 (p=0.209)	40.32±17.89 (p=0.974)	32.25±11.72 (p=0.130)	28.27±15.34 (p=0.660)	32.84±13.73 ***(p=0.035)***	27.34±7.38 (p=0.064)	41.47±10.46 (p=0.155)	50.54±10.18 (p=0.074)	57.98±15.69 (p=0.110)	61.50±12.10 (p=0.064)
Theta	PreStim	95.13±58.78	89.66±46.26	96.90±7.55	119.06±51.84	60.08±23.08	114.48±31.33	166.33±62.62	133.20±31.005	208.46±67.26	247.16±65.38	224.17±44.71
	Stim	62.18±28.73 (p=0.342)	69.38±31.99 (p=0.272)	75.17±33.20 ***(p=0.042)***	72.48±36.27 (p=0.128)	72.21±31.56 (p=0.326)	78.54±26.10 ***(p=0.036)***	88.33±32.38 (p=0.071)	109.64±28.18 (p=0.593)	151.41±48.02 (p=0.397)	171.03±50.66 (p=0.283)	129.65±29.43 (p=0.086)
	PostStim	85.92±34.38 (p=0.796)	61.02±34.80 (p=0.067)	89.35±49.81 (p=0.655)	74.72±34.73 (p=0.081)	61.41±33.45 (p=0.935)	120.14±74.06 (p=0.920)	102.74±63.85 ***(p=0.023)***	130.56±49.85 (p=0.953)	104.14±38.47 ***(p=0.049)***	110.09±31.21 ***(p=0.011)***	104.20±32.91 (p=0.067)
Alpha	PreStim	57.00±16.53	64.12±24.25	68.06±12.07	71.96±21.17	54.79±18.34	67.51±13.23	94.66±21.01	111.51±21.05	114.68±29.32	117.56±25.32	118.79±26.32
	Stim	49.67±14.73 (p=0.201)	56.18±22.65 (p=0.494)	55.49±19.40 (p=0.403)	40.94±10.53 (p=0.052)	95.93±61.45 (p=0.412)	115.09±68.56 (p=0.458)	88.97±25.96 (p=0.744)	133.34±48.37 (p=0.619)	122.50±44.51 (p=0.806)	111.63±43.28 (p=0.906)	121.98±42.51 (p=0.954)
	PostStim	54.91±18.77 (p=0.911)	43.02±14.82 (p=0.140)	41.31±8.69 (p=0.077)	52.16±15.94 (p=0.278)	47.07±23.88 (p=0.586)	54.08±26.00 (p=0.492)	44.05±19.59 (p=0.055)	57.85±19.57 ***(p=0.038)***	54.52±18.54 ***(p=0.010)***	63.11±20.07 (p=0.056)	60.53±19.43 (p=0.142)
Beta	PreStim	30.72±10.62	36.24±6.20	41.09±16.51	50.48±17.23	70.98±25.55	46.45±4.58	47.07±11.07	49.74±11.31	73.05±12.61	65.78±19.31	57.66±10.91
	Stim	32.41±9.45 (p=0.643)	30.40±9.18 (p=0.229)	28.72±7.22 (p=0.373)	28.41±7.17 (p=0.191)	44.37±12.86 (p=0.298)	32.52±8.44 (p=0.195)	35.11±9.74 (p=0.406)	37.73±9.13 (p=0.321)	38.22±8.89 ***(p=0.035)***	37.49±8.92 (p=0.151)	40.14±7.73 (p=0.166)
	PostStim	28.07±9.24 (p=0.423)	31.75±9.97 (p=0.541)	21.92±4.62 (p=0.175)	25.01±6.89 (p=0.203)	22.13±3.93 (p=0.087)	23.80±6.53 ***(p=0.008)***	23.97±4.92 (p=0.067)	30.45±8.44 (p=0.112)	22.46±4.92 ***(p=0.004)***	20.75±3.94 ***(p=0.026)***	30.99±7.03 (p=0.066)
Gamma	PreStim	5.41±1.54	5.69±1.33	6.37±1.10	7.11±1.34	4.97±1.39	7.43±1.91	7.88±1.74	7.20±1.36	9.49±1.59	10.14±2.17	9.72±1.08
	Stim	5.25±1.77 (p=0.535)	4.83±1.11 (p=0.370)	5.75±1.86 (p=0.601)	5.80±2.34 (p=0.378)	6.28±2.17 (p=0.253)	6.24±2.03 (p=0.162)	6.14±1.65 (p=0.141)	6.871±1.72 (p=0.827)	7.20±1.76 (p=0.152)	7.01±1.59 (p=0.068)	8.04±1.56 (p=0.150)
	PostStim	5.14±1.40 (p=0.393)	5.31±1.35 (p=0.678)	5.47±1.36 (p=0.260)	6.23±1.55 (p=0.329)	5.06±1.34 (p=0.848)	5.32±1.38 (p=0.058)	5.20±1.08 ***(p=0.031)***	5.90±0.85 (p=0.273)	6.01±1.03 ***(p=0.013)***	5.58±1.26 ***(p=0.020)***	6.90±0.95 ***(p=0.016)***

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table A.3. The effect of SN stimulations on the LFP of contralateral off-target areas under anesthesia.

		0.1v	0.5v	1v	1.5v	2v	2.5v	3v	3.5v	4v	4.5v	5v
	PreStim	212.28±61.67	204.68±24.97	262.73±67.71	254.57±42.59	335.31±66.26	318.77±72.48	262.84±40.27	342.10±46.42	417.61±62.20	382.85±73.11	421.55±63.08
Overall	Stim	180.57±38.41 (p=0.134)	157.66±40.62 (p=0.125)	194.81±45.11 (p=0.179)	262.04±65.23 (p=0.450)	323.14±54.56 (p=0.415)	392.94±98.63 (p=0.278)	256.24±93.37 (p=0.478)	351.88±116.00 (p=0.459)	375.12±63.34 (p=0.130)	425.56±104.45 (p=0.305)	444.63±74.13 (p=0.324)
	PostStim	171.12±42.61 (p=0.117)	199.48±61.92 (p=0.462)	188.31±62.45 (p=0.079)	264.48±93.34 (p=0.460)	360.78±111.63 (p=0.403)	311.61±96.68 (p=0.477)	230.68±49.09 (p=0.233)	274.20±61.78 (p=0.070)	227.00±58.80 ***(p=0.002)***	301.92±49.15 (p=0.093)	334.46±62.69 (p=0.135)
	PreStim	40.37±20.20	40.43±9.22	52.80±17.13	55.36±19.65	60.65±14.54	94.83±34.85	63.61±16.52	75.01±13.55	94.29±31.62	102.52±27.92	86.84±24.30
Delta	Stim	27.06±8.59 (p=0.324)	28.16±8.24 (p=0.228)	36.56±8.87 (p=0.294)	41.27±12.96 (p=0.451)	49.39±8.48 (p=0.441)	91.09±32.94 (p=0.950)	45.05±20.16 (p=0.600)	53.03±12.08 (p=0.060)	66.60±15.37 (p=0.499)	58.58±10.30 (p=0.247)	71.27±13.91 (p=0.633)
	PostStim	36.51±13.33 (p=0.781)	51.69±13.20 (p=0.295)	34.31±10.32 (p=0.057)	63.41±19.69 (p=0.787)	85.42±19.49 (p=0.290)	79.25±27.12 (p=0.697)	68.12±13.01 (p=0.684)	70.14±17.53 (p=0.779)	52.69±17.99 (p=0.243)	84.56±24.17 (p=0.69)	78.46±17.47 (p=0.800)
	PreStim	73.16±26.42	64.31±4.36	98.32±29.50	90.22±19.22	108.55±29.93	111.24±33.52	89.95±21.95	119.37±24.06	153.34±19.86	129.92±26.90	160.00±30.34
Theta	Stim	72.72±16.46 (p=0.976)	54.73±19.46 (p=0.678)	61.58±13.78 (p=0.250)	90.32±23.67 (p=0.996)	100.70±23.93 (p=0.821)	137.94±31.61 (p=0.578)	89.53±31.07 (p=0.992)	121.41±40.16 (p=0.926)	145.92±15.92 (p=0.669)	152.47±41.66 (p=0.540)	173.54±29.04 (p=0.612)
	PostStim	48.50±10.73 (p=0.257)	70.66±24.33 (p=0.814)	65.54±22.95 (p=0.216)	66.68±17.04 (p=0.215)	127.75±35.28 (p=0.613)	102.56±33.97 (p=0.859)	89.52±23.81 (p=0.982)	108.55±32.15 (p=0.535)	102.32±35.72 (p=0.082)	121.76±22.16 (p=0.613)	125.77±22.01 (p=0.338)
	PreStim	60.96±14.63	68.04±14.91	68.77±15.73	69.07±9.55	106.05±11.40	61.61±11.42	61.93±9.85	93.24±14.59	103.98±26.84	94.05±18.39	114.16±28.97
Alpha	Stim	53.45±13.75 (p=0.081)	51.64±13.52 (p=0.289)	66.46±22.38 (p=0.920)	73.03±18.23 (p=0.856)	108.52±21.44 (p=0.906)	96.51±33.94 (p=0.380)	73.79±34.43 (p=0.777)	107.19±43.86 (p=0.779)	113.92±40.05 (p=0.819)	140.59±47.34 (p=0.409)	124.89±31.28 (p=0.794)
	PostStim	53.05±14.17 (p=0.271)	51.90±20.20 (p=0.425)	58.00±25.40 (p=0.643)	66.16±23.35 (p=0.904)	73.71±25.95 (p=0.187)	77.47±21.50 (p=0.483)	42.80±9.81 (p=0.275)	61.54±17.73 (p=0.228)	38.41±9.93 (p=0.062)	55.45±15.19 (p=0.057)	83.23±27.07 (p=0.520)
	PreStim	31.70±7.35	24.94±4.27	35.35±8.67	32.45±2.08	50.91±13.15	41.63±9.72	38.04±5.44	44.35±4.07	56.06±11.60	46.51±8.45	49.18±5.18
Beta	Stim	21.29±3.49 (p=0.084)	17.49±3.08 (p=0.288)	24.06±6.11 (p=0.243)	41.95±11.31 (p=0.422)	52.79±14.40 (p=0.818)	51.12±20.49 (p=0.689)	40.61±24.82 (p=0.925)	57.43±29.94 (p=0.676)	37.53±14.43 (p=0.235)	62.04±23.78 (p=0.455)	61.22±19.75 (p=0.543)
	PostStim	24.80±6.99 (p=0.091)	19.97±5.32 (p=0.470)	23.26±8.95 ***(p=0.005)***	51.30±30.14 (p=0.556)	53.00±25.05 (p=0.925)	31.90±7.73 (p=0.389)	24.15±6.54 (p=0.181)	24.49±6.93 ***(p=0.046)***	25.70±8.49 (p=0.063)	30.08±8.31 ***(p=0.033)***	37.06±11.62 (p=0.392)
	PreStim	6.08±0.58	6.95±0.66	7.49±0.72	7.47±1.03	9.15±0.97	9.46±1.49	9.31±0.79	10.14±1.04	9.93±1.24	9.86±0.91	11.37±1.02
Gamma	Stim	6.06±0.65 (p=0.970)	5.64±0.73 (p=0.061)	6.15±0.45 (p=0.105)	15.47±6.17 (p=0.245)	11.74±2.94 (p=0.339)	16.27±7.01 (p=0.393)	7.26±2.34 (p=0.331)	12.82±4.34 (p=0.462)	11.16±2.97 (p=0.579)	11.87±3.73 (p=0.520)	13.72±4.87 (p=0.600)
	PostStim	8.25±1.60 (p=0.138)	5.27±0.55 ***(p<0.001)***	7.21±2.03 (p=0.856)	16.94±11.20 (p=0.436)	20.90±12.40 (p=0.384)	20.43±13.70 (p=0.470)	6.10±1.11 ***(p=0.027)***	9.49±1.34 (p=0.543)	7.88±1.71 (p=0.142)	10.05±1.84 (p=0.890)	9.93±1.81 (p=0.395)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table A.4. The effect of SN stimulations on the LFP of ipsilateral off-target areas under anesthesia.

		0.1v	0.5v	1v	1.5v	2v	2.5v	3v	3.5v	4v	4.5v	5v
Overall	PreStim	280.98±86.60	372.90±108.50	413.10±135.72	454.09±172.17	644.16±162.45	602.91±164.24	615.28±141.82	757.24±138.00	665.56±145.81	684.93±197.54	812.44±139.77
	Stim	271.80±92.20 (p=0.857)	328.30±99.06 (p=0.584)	421.74±165.00 (p=0.844)	456.51±163.50 (p=0.978)	519.18±166.25 (p=0.482)	702.51±153.41 (p=0.241)	680.01±168.67 (p=0.603)	792.11±197.29 (p=0.766)	794.47±180.93 (p=0.096)	882.38±262.90 (p=0.087)	821.78±226.76 (p=0.957)
	PostStim	286.32±101.37 (p=0.900)	319.26±108.77 (p=0.579)	375.96±115.60 (p=0.689)	383.16±116.36 (p=0.588)	393.78±96.80 (p=0.071)	372.48±76.04 (p=0.062)	499.01±104.22 (p=0.236)	520.51±135.06 ***(p=0.031)***	568.08±151.75 (p=0.059)	587.99±104.90 (p=0.357)	563.43±123.80 ***(p=0.017)***
Delta	PreStim	59.02±18.15	92.58±26.80	77.56±26.25	71.22±27.91	140.88±58.01	100.87±24.75	154.95±52.04	142.85±41.83	136.09±34.62	150.20±85.12	138.38±24.41
	Stim	55.99±21.35 (p=0.860)	80.26±25.57 (p=0.523)	82.79±28.20 (p=0.759)	110.89±39.24 (p=0.141)	112.98±27.03 (p=0.646)	169.37±46.37 (p=0.237)	108.56±20.13 (p=0.348)	128.98±31.19 (p=0.673)	128.91±30.75 (p=0.844)	126.00±26.39 (p=0.742)	123.14±29.80 (p=0.740)
	PostStim	50.41±19.22 (p=0.474)	113.33±49.72 (p=0.542)	97.20±35.29 (p=0.478)	98.41±30.04 (p=0.423)	113.86±25.57 (p=0.585)	96.33±23.29 (p=0.741)	177.87±39.85 (p=0.449)	142.55±42.67 (p=0.990)	168.59±50.32 (p=0.381)	152.56±42.27 (p=0.967)	169.33±59.09 (p=0.451)
Theta	PreStim	94.08±30.45	125.76±38.22	128.44±51.91	149.04±54.37	236.27±70.26	198.64±59.29	226.45±54.79	290.67±52.79	240.54±58.05	191.36±59.35	310.55±68.25
	Stim	77.01±28.98 (p=0.512)	114.91±40.64 (p=0.792)	150.74±61.54 (p=0.439)	187.24±74.99 (p=0.497)	233.34±107.72 (p=0.975)	281.46±97.07 (p=0.140)	305.11±85.86 (p=0.298)	379.71±108.18 (p=0.291)	338.80±90.51 (p=0.087)	454.05±166.37 (p=0.070)	408.92±139.63 (p=0.335)
	PostStim	99.12±40.78 (p=0.864)	88.48±26.69 (p=0.261)	121.80±43.65 (p=0.908)	140.75±51.15 (p=0.870)	130.46±42.22 (p=0.163)	152.25±34.75 (p=0.174)	173.81±50.99 (p=0.353)	229.52±83.06 (p=0.358)	249.82±80.05 (p=0.811)	241.72±60.51 (p=0.051)	210.88±70.22 ***(p=0.049)***
Alpha	PreStim	74.37±24.13	93.44±32.13	130.63±43.28	156.88±64.66	146.55±26.42	194.86±55.42	152.85±35.00	216.98±39.53	199.12±42.97	236.90±88.85	244.75±50.18
	Stim	83.36±29.61 (p=0.377)	70.13±20.79 (p=0.365)	124.41±51.02 (p=0.698)	95.05±32.79 (p=0.242)	98.43±31.82 (p=0.120)	163.11±43.28 (p=0.342)	193.78±55.50 (p=0.46)	195.37±60.04 (p=0.462)	206.75±53.55 (p=0.868)	209.98±68.18 (p=0.457)	209.66±77.86 (p=0.662)
	PostStim	77.45±26.39 (p=0.656)	69.13±22.18 (p=0.416)	94.19±31.46 (p=0.295)	81.17±25.85 (p=0.156)	88.88±21.42 ***(p=0.005)***	74.67±15.24 ***(p=0.041)***	96.72±25.59 (p=0.21)	87.10±18.31 ***(p=0.005)***	100.89±23.28 ***(p=0.023)***	125.03±29.32 (p=0.135)	129.27±31.11 ***(p=0.048)***
Beta	PreStim	41.04±13.73	46.39±14.13	62.20±19.08	64.20±25.66	92.08±24.91	89.70±24.43	58.50±10.61	89.39±21.94	72.96±16.95	85.39±25.05	98.81±24.64
	Stim	44.06±16.25 (p=0.604)	46.30±13.88 (p=0.986)	51.75±23.62 (p=0.242)	50.38±20.18 (p=0.156)	53.00±18.48 (p=0.064)	67.27±18.24 (p=0.119)	58.24±15.35 (p=0.983)	72.06±23.64 (p=0.514)	90.77±22.55 (p=0.170)	75.01±22.38 (p=0.213)	63.30±15.98 (p=0.147)
	PostStim	49.35±19.26 (p=0.253)	33.50±10.53 (p=0.154)	50.32±13.34 (p=0.427)	50.60±18.15 (p=0.482)	41.89±9.40 (p=0.051)	36.64±7.76 ***(p=0.028)***	37.73±6.84 (p=0.089)	47.81±13.88 (p=0.086)	36.04±8.00 ***(p=0.014)***	55.39±13.75 (p=0.104)	40.97±14.95 (p=0.075)
Gamma	PreStim	12.47±3.59	14.73±5.29	14.27±3.45	12.75±3.37	28.38±10.31	18.84±5.66	22.53±8.64	17.35±2.74	16.86±5.13	21.07±7.64	19.96±4.13
	Stim	11.38±3.36 (p=0.377)	16.70±6.75 (p=0.410)	12.04±4.01 (p=0.562)	12.95±4.10 (p=0.931)	21.43±7.38 (p=0.209)	21.30±6.93 (p=0.168)	14.33±3.34 (p=0.271)	15.99±4.12 (p=0.644)	29.24±13.95 (p=0.238)	17.33±4.54 (p=0.640)	16.76±3.25 (p=0.435)
	PostStim	9.99±2.74 (p=0.071)	14.82±6.32 (p=0.966)	12.44±3.41 (p=0.533)	12.22±3.58 (p=0.755)	18.68±6.31 (p=0.116)	12.59±3.32 (p=0.088)	12.88±3.00 (p=0.196)	13.54±2.27 (p=0.139)	12.75±2.88 (p=0.232)	13.29±2.68 (p=0.315)	12.98±2.43 (p=0.165)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Appendix B

Results in Table: the Effect of Mechanical Stimuli on the LFP of PL under Anesthesia

Table B.1. The effect of mechanical stimuli on the LFP of contralateral PL under anesthesia.

		Brush	Pressure	Pinch
	PreStim	538.93±174.30	395.70±42.32	586.02±181.78
Overall	Stim	666.27±232.32 (p=0.182)	515.33±127.67 (p=0.289)	395.74±144.02 ***<u>(p=0.049)</u>***
	PostSim	436.67±156.13 (p=0.083)	559.98±183.22 (p=0.346)	470.14±86.74 (p=0.323)
	PreStim	158.35±96.07	62.86±8.55	215.94±146.96
Delta	Stim	239.42±163.55 (p=0.277)	106.57±42.40 (p=0.295)	108.16±69.410 (p=0.233)
	PostSim	171.39±112.28 (p=0.599)	151.98±91.28 (p=0.338)	84.53±16.08 (p=0.383)
	PreStim	148.09±49.10	120.14±14.17	133.17±32.37
Theta	Stim	188.80±62.58 (p=0.247)	131.00±40.07 (p=0.793)	125.55±50.57 (p=0.836)
	PostSim	101.22±26.80 (p=0.097)	132.20±26.86 (p=0.718)	154.61±43.08 (p=0.433)
	PreStim	165.99±30.70	145.88±23.84	156.17±34.90
Alpha	Stim	169.84±24.69 (p=0.905)	197.13±52.89 (p=0.305)	108.84±32.19 (p=0.271)
	PostSim	107.09±25.44 (p=0.084)	203.27±65.48 (p=0.320)	167.32±34.71 (p=0.743)
	PreStim	55.62±12.75	58.00±9.14	71.58±13.36
Beta	Stim	57.65±10.18 (p=0.847)	66.22±13.50 (p=0.537)	45.82±9.37 (p=0.175)
	PostSim	48.71±14.05 (p=0.628)	61.80±14.11 (p=0.725)	55.91±10.85 (p=0.237)
	PreStim	10.88±4.04	8.81±1.11	9.16±1.39
Gamma	Stim	10.56±2.50 (p=0.895)	14.41±3.91 (p=0.212)	7.38±1.82 (p=0.332)
	PostSim	8.26±2.10 (p=0.242)	10.74±3.29 (p=0.506)	7.79±1.38 (p=0.485)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table B.2. The effect of mechanical stimuli on the LFP of ipsilateral PL under anesthesia.

		Brush	Pressure	Pinch
	PreStim	637.05±84.77	533.22±59.10	533.81±81.05
Overall	Stim	430.49±90.00 ***<u>(p=0.041)</u>***	624.48±82.84 (p=0.335)	459.92±67.49 ***<u>(p=0.010)</u>***
	PostSim	583.49±128.91 (p=0.563)	480.46±81.32 (p=0.495)	498.58±75.95 (p=0.603)
	PreStim	110.28±21.40	97.22±23.20	101.89±21.11
Delta	Stim	92.37±24.14 (p=0.377)	106.93±15.44 (p=0.693)	89.01±15.45 (p=0.298)
	PostSim	121.88±36.46 (p=0.663)	114.63±23.30 (p=0.097)	90.55±20.69 (p=0.488)
	PreStim	205.91±37.28	131.28±15.72	160.68±30.75
Theta	Stim	106.07±26.60 ***<u>(p=0.034)</u>***	183.95±21.86 (p=0.099)	134.21±24.43 (p=0.132)
	PostSim	150.64±29.52 (p=0.071)	139.62±21.27 (p=0.733)	133.11±18.89 (p=0.330)
	PreStim	218.50±30.20	216.87±31.50	171.83±27.27
Alpha	Stim	153.25±31.90 (p=0.160)	243.34±45.03 (p=0.623)	173.25±28.29 (p=0.948)
	PostSim	212.73±58.50 (p=0.919)	157.04±33.18 (p=0.236)	190.64±41.96 (p=0.649)
	PreStim	88.30±17.92	73.18±9.70	88.29±16.77
Beta	Stim	67.54±13.03 (p=0.301)	78.23±18.97 (p=0.801)	53.82±6.10 (p=0.061)
	PostSim	85.69±27.41 (p=0.915)	57.60±12.74 (p=0.327)	71.50±12.00 (p=0.350)
	PreStim	14.06±3.61	14.67±3.53	11.12±1.72
Gamma	Stim	11.25±1.98 (p=0.258)	12.02±2.89 (p=0.345)	9.63±1.73 (p=0.493)
	PostSim	12.55±2.58 (p=0.651)	11.57±2.46 (p=0.380)	12.78±3.16 (p=0.669)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Appendix C

Results in Table: the Effect of Formalin Injection on the LFP of PL under Anesthesia

Table C.1. The effect of formalin injection on the LFP of contralateral PL under anesthesia.

	Pre-Form	0min	5min	10min	15min	20min	25min	30min	35min	40min	45min
Overall	474.26±97.08	315.13±74.57 (p=0.170)	372.03±53.83 (p=0.104)	402.47±48.57 (p=0.529)	539.42±86.36 (p=0.666)	475.56±55.79 (p=0.991)	542.21±39.67 (p=0.542)	540.55±65.85 (p=0.602)	633.29±66.09 (p=0.166)	605.73±91.86 ***(p=0.033)***	473.93±75.88 (p=0.994)
Delta	101.02±44.46	74.05±17.01 (p=0.492)	86.78±21.27 (p=0.658)	70.07±12.35 (p=0.497)	110.06±16.14 (p=0.864)	101.62±19.59 (p=0.987)	103.34±15.47 (p=0.956)	122.24±30.09 (p=0.660)	96.27±24.50 (p=0.921)	113.07±28.23 (p=0.608)	88.51±15.40 (p=0.801)
Theta	130.96±17.88	99.85±26.27 (p=0.289)	117.52±33.27 (p=0.669)	119.33±13.75 (p=0.626)	168.70±24.44 (p=0.322)	125.95±16.68 (p=0.809)	140.57±22.45 (p=0.753)	167.14±28.02 (p=0.317)	183.21±38.69 (p=0.300)	174.10±22.13 (p=0.081)	136.75±25.09 (p=0.806)
Alpha	163.49±30.01	93.08±29.43 (p=0.148)	118.74±21.68 (p=0.125)	155.50±24.57 (p=0.851)	171.94±35.47 (p=0.866)	161.35±29.34 (p=0.965)	204.97±24.77 (p=0.242)	171.86±21.62 (p=0.806)	247.92±26.69 (p=0.060)	207.13±37.34 (p=0.074)	166.77±37.09 (p=0.890)
Beta	70.79±12.06	41.08±12.53 (p=0.148)	42.75±3.94 (p=0.095)	51.27±12.02 (p=0.202)	77.39±17.42 (p=0.749)	66.23±12.74 (p=0.828)	80.30±11.30 (p=0.661)	66.66±10.80 (p=0.838)	89.80±8.90 ***(p=0.021)***	96.22±18.98 (p=0.215)	70.05±17.68 (p=0.919)
Gamma	8.01±1.02	7.06±1.58 (p=0.666)	6.23±0.59 (p=0.179)	6.30±0.62 (p=0.241)	11.33±2.00 (p=0.206)	20.40±11.63 (p=0.343)	13.04±1.78 ***(p=0.048)***	12.650±2.68 (p=0.233)	16.10±3.57 (p=0.096)	15.22±2.29 ***(p=0.027)***	11.86±2.76 (p=0.226)

Note: Pre-Form: pre-formalin. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding Pre-Form.

Table C.2. The effect of formalin injection on the LFP of ipsilateral PL under anesthesia.

	Pre-Form	0min	5min	10min	15min	20min	25min	30min	35min	40min	45min
Overall	697.88±122.60	442.74±87.32	685.17±68.54	639.19±68.14	574.19±55.09	721.16±101.35	526.55±72.80	626.44±85.99	638.46±76.83	609.75±80.67	722.35±84.48
		(p=0.016)	(p=0.898)	(p=0.607)	(p=0.241)	(p=0.846)	(p=0.133)	(p=0.635)	(p=0.666)	(p=0.558)	(p=0.849)
Delta	99.12±18.56	83.43±16.04	123.88±26.64	134.31±28.47	103.62±12.69	145.70±31.26	127.17±35.03	129.05±36.88	138.41±26.24	138.93±27.97	139.70±26.23
		(p=0.422)	(p=0.116)	(p=0.092)	(p=0.718)	***(p=0.021)***	(p=0.367)	(p=0.381)	***(p=0.040)***	(p=0.102)	***(p=0.042)***
Theta	170.17±29.98	150.40±38.59	186.57±37.42	146.38±17.32	137.46±23.53	197.43±22.92	135.70±19.04	166.73±38.00	178.54±17.30	175.72±26.55	212.58±34.17
		(p=0.544)	(p=0.476)	(p=0.259)	(p=0.187)	(p=0.243)	***(p=0.043)***	(p=0.916)	(p=0.740)	(p=0.869)	(p=0.084)
Alpha	296.41±73.85	148.30±37.43	254.45±34.01	241.09±22.26	215.38±28.35	246.20±44.06	171.88±30.34	234.20±16.29	211.01±23.97	200.27±28.98	277.43±30.35
		(p=0.017)	(p=0.628)	(p=0.505)	(p=0.305)	(p=0.565)	(p=0.158)	(p=0.460)	(p=0.306)	(p=0.308)	(p=0.822)
Beta	115.21±21.20	51.62±9.46	110.18±15.66	103.80±18.19	105.71±21.66	117.14±24.29	82.25±19.29	85.49±9.79	95.71±18.37	84.97±19.65	81.73±10.27
		(p=0.003)	(p=0.850)	(p=0.590)	(p=0.722)	(p=0.954)	(p=0.216)	(p=0.284)	(p=0.489)	(p=0.243)	(p=0.219)
Gamma	16.97±4.58	9.00±1.34	10.09±1.47	13.61±2.26	12.02±2.74	14.69±2.28	9.55±1.30	10.97±1.36	14.80±3.92	9.85±1.56	10.91±1.75
		(p=0.060)	(p=0.105)	(p=0.269)	(p=0.264)	(p=0.585)	(p=0.098)	(p=0.255)	(p=0.619)	(p=0.200)	(p=0.185)

Note: Pre-Form: pre-formalin. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding Pre-Form.

Appendix D

Results in Table: the Effect of SN Stimulations on the LFP of PL in Freely Moving animal

Table D.1. The effect of SN stimulations on the LFP of contralateral PL in freely moving animal (with all data points included).

		PreStim	Stim	PostStim-a	PostStim-b	PostStim-c	PostStim-d	PostStim-e
	0.1v (n=9)	160.06±5.31	155.63±11.11 (p=0.675)	170.15±13.61 (p=0.471)	189.62±11.66 ***(p=0.020)***	384.92±220.18 (p=0.330)	661.25±337.35 (p=0.175)	707.50±357.58 (p=0.163)
	0.5v (n=9)	433.43±236.04	1105.32±507.70 (p=0.200)	731.89±360.31 (p=0.405)	842.59±453.74 (p=0.367)	497.17±224.31 (p=0.796)	215.22±51.93 (p=0.275)	278.65±101.56 (p=0.302)
	1v (n=8)	177.87±15.05	1594.89±780.35 (p=0.117)	1960.08±696.21 ***(p=0.039)***	973.04±422.26 (p=0.105)	512.71±191.29 (p=0.125)	970.49±423.97 (p=0.105)	872.37±438.86 (p=0.160)
	1.5v (n=9)	436.24±222.13	3231.20±817.36 ***(p=0.014)***	1333.63±491.82 (p=0.178)	1179.92±474.91 (p=0.239)	337.58±90.48 (p=0.707)	502.54±264.01 (p=0.862)	390.34±151.17 (p=0.879)
Overall	2v (n=9)	704.74±509.08	4408.69±794.30 ***(p=0.002)***	1991.08±489.55 (p=0.146)	763.38±279.19 (p=0.917)	477.59±142.41 (p=0.690)	533.57±276.86 (p=0.780)	478.93±216.79 (p=0.708)
	2.5v (n=8)	197.10±32.29	4749.11±699.18 ***(p<0.001)***	2152.03±483.04 ***(p=0.005)***	1363.30±431.88 ***(p=0.030)***	1150.26±434.18 (p=0.061)	434.45±201.94 (p=0.256)	319.48±67.25 (p=0.074)
	3v (n=5)	441.04±240.14	4785.63±837.15 ***(p=0.006)***	2194.97±950.20 (p=0.165)	857.09±453.66 (p=0.513)	726.43±313.77 (p=0.362)	658.87±283.33 (p=0.094)	1228.84±879.36 (p=0.471)
	3.5v (n=3)	198.93±44.89	3555.10±418.73 ***(p=0.014)***	679.36±72.65 (p=0.052)	420.30±113.41 (p=0.184)	761.64±546.85 (p=0.383)	211.48±45.03 (p=0.060)	339.85±76.39 (p=0.321)
	4v (n=3)	189.08±29.81	4570.04±1101.82 (p=0.060)	1037.38±450.39 (p=0.219)	384.64±144.21 (p=0.338)	1035.76±756.98 (p=0.382)	1594.20±1392.90 (p=0.420)	1035.14±848.18 (p=0.425)
	4.5v (n=3)	1068.50±905.51	4718.18±460.41 ***(p=0.015)***	2644.90±772.06 (p=0.300)	543.00±189.01 (p=0.580)	659.47±417.52 (p=0.493)	547.64±333.17 (p=0.461)	652.71±390.09 (p=0.509)
	5v (n=2)	157.76±5.95	4583.74±192.17 ***(p=0.028)***	1327.86±690.30 (p=0.342)	512.30±107.82 (p=0.198)	388.02±83.85 (p=0.237)	253.39±110.37 (p=0.562)	226.58±20.12 (p=0.231)
	0.1v (n=9)	18.26±1.88	16.63±2.12 (p=0.619)	20.39±2.74 (p=0.553)	34.59±4.70 ***(p=0.012)***	61.96±41.36 (p=0.335)	179.37±103.31 (p=0.161)	211.42±117.79 (p=0.142)
	0.5v (n=9)	70.71±44.98	325.04±191.35 (p=0.195)	165.40±92.73 (p=0.277)	199.08±137.30 (p=0.212)	105.50±59.02 (p=0.566)	31.08±9.14 (p=0.327)	66.38±39.27 (p=0.531)
	1v (n=8)	17.14±1.86	333.94±150.09 (p=0.073)	608.35±235.45 ***(p=0.041)***	292.64±176.74 (p=0.162)	90.90±33.99 (p=0.069)	253.81±128.56 (p=0.110)	214.55±113.30 (p=0.127)
	1.5v (n=9)	86.52±53.00	708.89±279.45 (p=0.072)	269.81±137.04 (p=0.276)	219.05±89.69 (p=0.285)	87.69±32.62 (p=0.987)	73.36±23.15 (p=0.833)	123.39±62.60 (p=0.698)
Delta	2v (n=9)	260.11±223.92	879.90±205.72 ***(p=0.028)***	545.61±123.24 (p=0.348)	140.50±55.40 (p=0.567)	140.56±69.67 (p=0.637)	150.61±112.85 (p=0.684)	128.93±96.27 (p=0.620)
	2.5v (n=8)	28.49±8.89	1165.79±226.11 ***(p=0.002)***	541.77±119.49 ***(p=0.004)***	447.95±168.79 ***(p=0.042)***	318.73±146.80 (p=0.089)	94.01±48.94 (p=0.166)	75.17±21.69 ***(p=0.027)***
	3v (n=5)	100.11±70.33	1135.44±236.11 ***(p=0.013)***	438.78±115.46 ***(p=0.020)***	145.14±66.08 (p=0.704)	184.42±100.68 (p=0.356)	305.16±194.49 (p=0.188)	263.13±170.11 (p=0.475)
	3.5v (n=3)	33.74±12.81	962.84±156.66 ***(p=0.024)***	216.26±38.40 (p=0.066)	86.48±46.18 (p=0.449)	177.37±142.16 (p=0.389)	27.05±6.89 (p=0.435)	112.40±57.34 (p=0.357)
	4v (n=3)	22.39±5.68	977.43±380.54 (p=0.132)	245.09±148.19 (p=0.272)	74.02±26.79 (p=0.250)	341.22±271.47 (p=0.369)	356.96±327.32 (p=0.420)	239.33±216.75 (p=0.432)
	4.5v (n=3)	171.37±142.89	883.98±164.59 (p=0.134)	1227.72±484.89 (p=0.192)	158.61±59.39 (p=0.931)	273.85±225.12 (p=0.339)	219.64±178.36 (p=0.319)	250.22±187.16 (p=0.238)
	5v (n=2)	24.33±2.81	1348.10±275.39 (p=0.132)	405.92±255.86 (p=0.379)	174.67±61.79 (p=0.258)	109.60±25.39 (p=0.203)	57.05±28.62 (p=0.487)	20.66±5.48 (p=0.400)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table D.1. *Continued*

	0.1v (n=9)	44.58±2.81	34.54±4.50 (p=0.124)	43.25±5.70 (p=0.842)	46.94±7.39 (p=0.690)	127.22±87.12 (p=0.364)	283.28±174.63 (p=0.208)	246.56±139.43 (p=0.184)
	0.5v (n=9)	189.29±134.44	343.87±194.54 (p=0.494)	343.21±195.63 (p=0.442)	339.26±234.04 (p=0.574)	213.96±115.10 (p=0.841)	71.40±26.09 (p=0.319)	85.00±39.64 (p=0.310)
	1v (n=8)	46.45±6.02	519.04±264.37 (p=0.120)	761.61±302.73 (p=0.051)	337.43±167.92 (p=0.124)	167.51±87.47 (p=0.200)	366.32±183.80 (p=0.124)	280.31±148.82 (p=0.162)
	1.5v (n=9)	206.80±142.30	935.18±283.03 (p=0.082)	346.26±125.08 (p=0.544)	682.92±317.34 (p=0.251)	90.54±31.44 (p=0.467)	120.38±61.80 (p=0.609)	133.56±67.80 (p=0.674)
Theta	2v (n=9)	200.71±153.61	1399.14±240.05 ***(p=0.002)***	826.19±192.96 (p=0.057)	256.02±93.12 (p=0.763)	109.14±34.44 (p=0.587)	151.14±92.19 (p=0.794)	113.27±63.87 (p=0.631)
	2.5v (n=8)	49.60±10.37	1193.43±269.46 ***(p=0.004)***	1029.67±273.17 ***(p=0.010)***	486.83±176.43 ***(p=0.042)***	452.88±196.30 (p=0.077)	188.35±129.40 (p=0.315)	89.98±27.35 (p=0.175)
	3v (n=5)	101.96±52.56	1233.72±178.00 ***(p=0.002)***	752.05±298.99 (p=0.112)	204.47±69.27 (p=0.364)	269.84±140.05 (p=0.188)	171.53±70.66 (p=0.118)	315.45±232.21 (p=0.455)
	3.5v (n=3)	40.47±18.48	1234.96±357.16 (p=0.080)	177.06±17.15 ***(p=0.037)***	107.88±36.00 (p=0.123)	228.18±187.44 (p=0.383)	50.45±18.23 (p=0.064)	78.23±34.62 (p=0.509)
	4v (n=3)	38.79±13.57	1473.73±328.62 ***(p=0.046)***	456.31±251.07 (p=0.240)	124.40±65.02 (p=0.239)	439.34±353.00 (p=0.359)	397.38±357.44 (p=0.407)	263.81±226.38 (p=0.401)
	4.5v (n=3)	608.62±579.31	1332.93±73.46 (p=0.222)	937.49±283.88 (p=0.550)	183.30±75.57 (p=0.515)	181.37±132.60 (p=0.441)	166.87±117.20 (p=0.440)	186.64±122.02 (p=0.454)
	5v (n=2)	21.55±1.42	1791.34±78.80 ***(p=0.028)***	625.89±325.47 (p=0.316)	127.17±31.28 (p=0.191)	108.65±57.72 (p=0.380)	58.74±37.02 (p=0.511)	64.27±3.03 (p=0.066)
	0.1v (n=9)	28.20±1.99	26.64±2.52 (p=0.381)	33.18±2.94 (p=0.190)	29.98±5.46 (p=0.779)	77.03±48.03 (p=0.332)	94.59±46.29 (p=0.182)	141.27±79.63 (p=0.189)
	0.5v (n=9)	76.19±35.41	244.72±107.89 (p=0.097)	107.24±52.61 (p=0.567)	164.04±116.79 (p=0.485)	77.05±35.67 (p=0.984)	34.72±9.35 (p=0.156)	42.11±12.64 (p=0.228)
	1v (n=8)	38.37±11.50	461.13±264.69 (p=0.160)	333.88±129.66 (p=0.064)	163.86±76.92 (p=0.168)	99.48±52.95 (p=0.304)	133.09±60.82 (p=0.188)	120.44±62.34 (p=0.237)
	1.5v (n=9)	62.32±20.50	888.46±262.46 ***(p=0.013)***	340.93±167.18 (p=0.155)	152.07±70.02 (p=0.299)	63.16±22.99 (p=0.981)	186.03±152.72 (p=0.459)	48.23±11.97 (p=0.606)
Alpha	2v (n=9)	85.83±51.97	1265.44±322.11 ***(p=0.007)***	360.31±139.69 (p=0.116)	201.62±100.78 (p=0.338)	76.19±21.51 (p=0.879)	105.30±57.16 (p=0.820)	99.73±47.18 (p=0.861)
	2.5v (n=8)	27.49±3.58	1218.69±320.42 ***(p=0.007)***	355.41±109.23 ***(p=0.022)***	193.81±64.84 ***(p=0.039)***	179.80±87.43 (p=0.129)	44.88±13.15 (p=0.198)	54.55±12.75 (p=0.064)
	3v (n=5)	97.95±61.78	1186.06±316.54 ***(p=0.017)***	428.55±266.55 (p=0.320)	143.50±84.29 (p=0.725)	113.78±43.34 (p=0.841)	71.36±22.14 (p=0.656)	225.50±170.51 (p=0.559)
	3.5v (n=3)	35.27±3.08	857.85±81.04 ***(p=0.010)***	94.41±14.43 (p=0.061)	99.98±45.99 (p=0.314)	235.54±195.78 (p=0.418)	30.88±10.14 (p=0.744)	41.19±8.45 (p=0.633)
	4v (n=3)	26.12±2.03	1335.45±266.99 ***(p=0.039)***	157.67±58.10 (p=0.147)	66.48±27.65 (p=0.256)	107.28±72.21 (p=0.367)	302.40±269.94 (p=0.411)	145.79±103.33 (p=0.359)
	4.5v (n=3)	125.65±101.70	1481.36±451.50 (p=0.061)	285.98±69.26 (p=0.151)	77.71±37.81 (p=0.569)	93.39±56.21 (p=0.579)	55.81±21.82 (p=0.491)	113.07±64.98 (p=0.786)
	5v (n=2)	28.94±2.96	711.85±13.42 ***(p=0.010)***	118.57±74.25 (p=0.428)	79.63±3.28 ***(p=0.004)***	57.89±11.41 (p=0.181)	36.01±16.05 (p=0.685)	47.65±17.10 (p=0.412)

Table D.1. *Continued*

	0.1v (n=9)	38.17±1.70	44.68±5.24 (p=0.260)	38.95±2.54 (p=0.813)	42.98±3.12 (p=0.070)	64.13±22.27 (p=0.271)	55.09±12.51 (p=0.216)	65.04±18.37 (p=0.195)
	0.5v (n=9)	54.33±12.63	105.30±30.06 (p=0.123)	68.09±17.06 (p=0.432)	89.89±40.35 (p=0.404)	58.20±13.73 (p=0.814)	39.70±5.70 (p=0.118)	42.62±6.34 (p=0.217)
	1v (n=8)	44.04±5.27	182.44±78.90 (p=0.136)	146.07±43.92 (p=0.065)	92.78±29.83 (p=0.189)	66.33±17.74 (p=0.252)	103.07±42.55 (p=0.216)	129.01±74.69 (p=0.299)
	1.5v (n=9)	42.39±6.86	443.08±170.45 (p=0.051)	113.74±33.48 (p=0.090)	77.76±15.62 (p=0.096)	49.13±7.33 (p=0.399)	67.92±26.32 (p=0.387)	42.99±6.04 (p=0.933)
Beta	2v (n=9)	98.17±59.40	626.00±177.77 ***(p=0.020)***	174.83±46.03 (p=0.389)	104.95±34.10 (p=0.922)	67.57±10.92 (p=0.634)	77.33±17.15 (p=0.740)	87.60±38.56 (p=0.889)
	2.5v (n=8)	50.03±9.91	729.91±211.81 ***(p=0.016)***	139.76±23.42 ***(p=0.013)***	112.32±28.27 (p=0.099)	95.65±22.60 (p=0.098)	55.47±9.16 (p=0.651)	48.64±6.53 (p=0.854)
	3v (n=5)	83.06±39.23	762.36±273.78 (p=0.072)	224.46±143.46 (p=0.435)	146.71±85.78 (p=0.584)	73.98±23.95 (p=0.862)	55.20±5.96 (p=0.515)	196.86±144.34 (p=0.524)
	3.5v (n=3)	52.83±10.98	360.50±57.74 ***(p=0.023)***	98.91±23.70 (p=0.277)	56.82±10.05 (p=0.305)	67.66±14.09 ***(p=0.042)***	57.50±4.85 (p=0.551)	50.58±6.34 (p=0.752)
	4v (n=3)	50.08±12.89	574.52±140.66 (p=0.075)	97.16±28.70 (p=0.360)	63.18±18.03 (p=0.683)	82.32±36.44 (p=0.539)	209.33±150.34 (p=0.416)	81.23±29.96 (p=0.506)
	4.5v (n=3)	92.72±50.79	667.43±137.52 (p=0.070)	108.56±31.00 (p=0.835)	66.33±15.81 (p=0.610)	60.51±5.11 (p=0.587)	55.09±9.09 (p=0.479)	57.96±9.60 (p=0.513)
	5v (n=2)	48.19±1.29	507.27±30.06 ***(p=0.043)***	88.26±37.40 (p=0.467)	54.63±1.22 (p=0.236)	53.51±3.72 (p=0.480)	54.16±16.19 (p=0.757)	52.31±2.84 (p=0.229)
	0.1v (n=9)	30.86±2.94	33.15±2.59 (p=0.254)	34.38±2.91 (p=0.124)	35.14±3.48 (p=0.069)	54.58±21.84 (p=0.259)	48.92±13.06 (p=0.140)	43.23±6.88 ***(p=0.047)***
	0.5v (n=9)	42.91±10.37	86.39±34.27 (p=0.262)	47.96±8.06 (p=0.493)	50.33±7.17 (p=0.459)	42.46±5.94 (p=0.944)	38.32±4.92 (p=0.459)	42.55±8.73 (p=0.967)
	1v (n=8)	31.87±3.15	98.35±31.00 (p=0.077)	110.18±48.60 (p=0.148)	86.33±36.48 (p=0.172)	88.48±41.42 (p=0.205)	114.20±73.69 (p=0.296)	128.06±83.75 (p=0.284)
	1.5v (n=9)	38.22±4.89	255.59±104.20 (p=0.073)	262.88±205.25 (p=0.306)	48.11±4.98 (p=0.101)	47.07±6.12 (p=0.090)	54.86±12.95 (p=0.200)	42.17±6.77 (p=0.572)
Gamma	2v (n=9)	59.92±20.97	238.21±53.66 ***(p=0.006)***	84.14±16.18 (p=0.370)	60.29±9.36 (p=0.982)	84.13±35.51 (p=0.548)	49.19±8.58 (p=0.465)	49.40±6.60 (p=0.598)
	2.5v (n=8)	39.96±6.61	352.21±119.56 ***(p=0.035)***	105.49±19.65 ***(p=0.011)***	117.28±45.31 (p=0.138)	99.85±40.16 (p=0.182)	53.19±7.71 ***(p=0.028)***	54.53±7.33 ***(p=0.002)***
	3v (n=5)	57.96±17.32	468.06±232.17 (p=0.157)	351.13±252.25 (p=0.318)	217.19±155.25 (p=0.378)	84.41±32.61 (p=0.517)	55.62±7.45 (p=0.860)	227.91±167.09 (p=0.381)
	3.5v (n=3)	36.63±5.06	138.95±10.24 ***(p=0.003)***	92.73±21.76 (p=0.112)	69.14±8.90 (p=0.103)	52.89±11.75 (p=0.153)	45.59±6.81 (p=0.085)	57.46±7.80 ***(p=0.023)***
	4v (n=3)	51.70±19.87	208.90±47.72 (p=0.133)	81.16±2.87 (p=0.311)	56.57±11.57 (p=0.846)	65.60±24.65 (p=0.729)	328.13±288.00 (p=0.448)	304.98±272.57 (p=0.461)
	4.5v (n=3)	70.15±31.23	352.48±42.81 ***(p=0.028)***	85.16±6.48 (p=0.706)	57.05±11.32 (p=0.579)	50.36±3.59 (p=0.549)	50.22±9.68 (p=0.463)	44.82±8.68 (p=0.379)
	5v (n=2)	34.75±5.96	225.20±12.24 (p=0.061)	89.22±2.68 ***(p=0.038)***	76.21±12.69 (p=0.269)	58.38±6.95 ***(p=0.027)***	47.43±12.49 (p=0.617)	41.69±2.64 (p=0.568)

Table D.2. The effect of SN stimulations on the LFP of ipsilateral PL in freely moving animal (with all data points included).

		PreStim	Stim	PostStim-a	PostStim-b	PostStim-c	PostStim-d	PostStim-e
	0.1v (n=9)	189.61±11.30	180.28±12.87 (p=0.577)	174.63±7.84 (p=0.398)	245.21±58.15 (p=0.413)	406.37±210.02 (p=0.343)	283.71±85.46 (p=0.331)	165.66±8.13 (p=0.172)
	0.5v (n=9)	192.90±10.27	897.80±296.98 ***<u>(p=0.048)</u>***	385.61±157.03 (p=0.263)	238.93±42.18 (p=0.288)	188.69±7.95 (p=0.757)	179.89±9.99 (p=0.502)	174.89±4.12 (p=0.144)
	1v (n=8)	255.51±64.17	2642.62±743.05 ***<u>(p=0.018)</u>***	1020.64±638.52 (p=0.281)	706.24±524.69 (p=0.432)	705.86±502.44 (p=0.415)	984.70±800.78 (p=0.401)	518.34±296.63 (p=0.435)
	1.5v (n=9)	200.23±12.64	3544.19±509.86 ***<u>(p<0.001)</u>***	1556.82±374.41 ***<u>(p=0.007)</u>***	1197.98±738.86 (p=0.214)	1048.71±565.52 (p=0.170)	1683.59±724.56 (p=0.073)	752.08±313.04 (p=0.110)
Overall	2v (n=8)	196.73±18.28	5036.28±545.52 ***<u>(p<0.001)</u>***	1902.21±425.38 ***<u>(p=0.005)</u>***	469.57±174.20 (p=0.171)	401.29±74.36 ***<u>(p=0.027)</u>***	724.76±328.58 (p=0.159)	636.23±280.85 (p=0.160)
	2.5v (n=8)	209.17±21.52	5289.60±615.92 ***<u>(p<0.001)</u>***	1802.66±491.81 ***<u>(p=0.015)</u>***	1053.04±332.19 ***<u>(p=0.042)</u>***	770.01±293.88 (p=0.086)	740.89±257.48 (p=0.065)	1041.67±351.23 ***<u>(p=0.046)</u>***
	3v (n=5)	627.65±449.64	5704.48±968.76 ***<u>(p=0.003)</u>***	2248.11±914.26 (p=0.246)	1372.45±623.38 (p=0.336)	553.22±213.23 (p=0.782)	1374.56±681.09 (p=0.176)	1463.24±790.39 (p=0.169)
	3.5v (n=4)	193.30±19.89	5325.44±619.47 ***<u>(p=0.003)</u>***	945.46±355.22 (p=0.114)	238.92±28.56 (p=0.131)	207.53±18.10 (p=0.162)	442.31±251.00 (p=0.370)	214.29±47.12 (p=0.614)
	4v (n=4)	200.89±29.05	4849.68±982.36 ***<u>(p=0.017)</u>***	1395.18±566.31 (p=0.115)	989.64±741.68 (p=0.372)	520.97±118.94 (p=0.076)	205.89±15.34 (p=0.853)	218.15±18.64 (p=0.684)
	4.5v (n=2)	175.73±14.24	5430.92±1188.45 ***<u>(p=0.049)</u>***	2090.82±389.02 ***<u>(p=0.039)</u>***	1396.36±670.58 (p=0.216)	759.93±435.63 (p=0.306)	923.48±735.67 (p=0.482)	212.65±28.59 (p=0.530)
	5v (n=2)	190.49±25.58	5084.38±1411.74 (p=0.176)	1806.76±853.14 (p=0.301)	311.57±35.02 (p=0.050)	462.12±201.83 (p=0.366)	222.39±51.90 (p=0.439)	1311.90±1064.16 (p=0.476)
	0.1v (n=9)	21.25±3.99	21.06±2.95 (p=0.964)	21.07±2.32 (p=0.965)	38.17±17.16 (p=0.398)	47.34±24.82 (p=0.352)	60.90±37.84 (p=0.346)	22.31±2.99 (p=0.780)
	0.5v (n=9)	24.61±4.33	272.62±87.44 ***<u>(p=0.024)</u>***	63.20±30.79 (p=0.229)	45.23±11.65 ***<u>(p=0.045)</u>***	26.72±2.56 (p=0.669)	23.38±3.54 (p=0.871)	17.53±2.17 (p=0.267)
	1v (n=8)	51.35±24.23	709.65±161.61 ***<u>(p=0.006)</u>***	357.85±231.81 (p=0.234)	199.32±118.75 (p=0.269)	145.38±122.32 (p=0.487)	163.24±136.58 (p=0.456)	131.00±63.90 (p=0.301)
	1.5v (n=9)	28.50±4.43	963.81±221.01 ***<u>(p=0.003)</u>***	419.66±126.18 ***<u>(p=0.014)</u>***	232.97±139.42 (p=0.181)	252.64±112.07 (p=0.080)	523.52±199.40 ***<u>(p=0.037)</u>***	162.01±68.77 (p=0.086)
Delta	2v (n=9)	30.07±7.02	1048.26±185.11 ***<u>(p=0.001)</u>***	673.96±162.11 ***<u>(p=0.005)</u>***	144.42±72.36 (p=0.172)	110.94±35.59 (p=0.072)	253.14±121.92 (p=0.120)	150.97±82.51 (p=0.188)
	2.5v (n=8)	35.38±5.84	1451.26±158.13 ***<u>(p<0.001)</u>***	466.11±193.30 (p=0.070)	271.11±184.00 (p=0.252)	215.75±96.17 (p=0.106)	359.70±174.62 (p=0.107)	327.14±195.80 (p=0.187)
	3v (n=5)	90.55±65.09	1294.31±241.36 ***<u>(p=0.008)</u>***	690.68±305.34 (p=0.151)	491.30±207.62 (p=0.120)	129.25±40.11 (p=0.476)	383.73±201.53 (p=0.140)	613.33±344.92 (p=0.156)
	3.5v (n=3)	27.76±2.37	1087.66±233.97 ***<u>(p=0.020)</u>***	249.87±104.65 (p=0.121)	33.48±10.72 (p=0.638)	27.74±4.94 (p=0.996)	77.40±45.10 (p=0.331)	31.67±15.04 (p=0.779)
	4v (n=3)	36.73±17.83	703.45±89.29 ***<u>(p=0.005)</u>***	544.67±261.33 (p=0.135)	199.99±140.32 (p=0.360)	149.99±57.25 (p=0.159)	26.71±4.43 (p=0.545)	36.69±8.69 (p=0.999)
	4.5v (n=3)	32.81±8.86	1255.90±277.75 ***<u>(p=0.048)</u>***	510.91±262.54 (p=0.219)	450.7±278.99 (p=0.283)	138.70±54.26 (p=0.209)	499.86±466.60 (p=0.489)	64.85±23.37 (p=0.554)
	5v (n=2)	36.58±19.98	908.45±421.17 (p=0.298)	285.80±158.96 (p=0.324)	51.20±5.69 (p=0.670)	112.12±70.54 (p=0.376)	31.02±14.39 (p=0.501)	213.97±150.16 (p=0.403)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table D.2. *Continued*

Theta	0.1v (n=9)	55.59±7.60	50.24±9.61 (p=0.536)	41.48±4.57 (p=0.123)	76.58±23.94 (p=0.485)	174.82±117.04 (p=0.351)	80.41±27.25 (p=0.450)	38.32±2.78 ***(p=0.047)***
	0.5v (n=9)	55.10±5.66	259.24±89.97 (p=0.059)	117.04±62.02 (p=0.369)	70.96±21.53 (p=0.527)	44.97±4.67 (p=0.060)	46.51±6.33 (p=0.288)	46.87±5.99 (p=0.150)
	1v (n=8)	76.39±27.44	900.77±238.28 ***(p=0.011)***	391.49±186.95 (p=0.149)	224.87±138.98 (p=0.347)	191.13±135.29 (p=0.449)	238.08±183.96 (p=0.426)	204.62±98.27 (p=0.278)
	1.5v (n=9)	57.43±7.87	931.83±175.21 ***(p=0.001)***	497.04±94.37 ***(p=0.002)***	410.52±230.39 (p=0.166)	394.16±223.68 (p=0.170)	510.17±212.22 (p=0.066)	266.48±146.19 (p=0.189)
	2v (n=9)	52.82±12.46	1406.33±169.06 ***(p<0.001)***	707.02±162.62 ***(p=0.005)***	143.22±61.81 (p=0.200)	134.66±37.00 (p=0.052)	239.87±138.79 (p=0.233)	257.13±151.37 (p=0.227)
	2.5v (n=8)	47.22±7.13	1432.77±199.60 ***(p<0.001)***	562.98±216.52 (p=0.056)	288.99±132.42 (p=0.122)	256.33±127.29 (p=0.137)	177.00±59.94 (p=0.054)	435.62±202.35 (p=0.105)
	3v (n=5)	176.89±130.33	1304.13±282.26 ***(p=0.004)***	918.39±383.74 (p=0.187)	501.93±264.33 (p=0.284)	189.00±101.79 (p=0.737)	539.19±288.97 (p=0.156)	486.11±286.58 (p=0.173)
	3.5v (n=3)	46.49±10.96	1485.42±347.35 ***(p=0.024)***	319.17±125.08 (p=0.108)	67.41±18.55 (p=0.381)	49.23±10.58 (p=0.677)	176.47±138.72 (p=0.385)	58.15±24.04 (p=0.482)
	4v (n=3)	47.77±4.84	1313.62±220.82 ***(p=0.010)***	497.93±195.80 (p=0.100)	398.93±341.48 (p=0.384)	177.12±64.64 (p=0.148)	52.00±14.36 (p=0.748)	58.14±7.45 (p=0.425)
	4.5v (n=3)	27.89±5.19	1209.03±119.56 ***(p=0.010)***	620.48±60.24 ***(p=0.009)***	573.67±346.97 (p=0.254)	214.37±115.79 (p=0.262)	213.76±157.78 (p=0.462)	39.37±14.48 (p=0.681)
	5v (n=2)	43.45±8.41	1083.56±214.04 (p=0.124)	921.39±401.10 (p=0.268)	132.72±41.22 (p=0.224)	201.91±115.14 (p=0.377)	76.02±28.95 (p=0.358)	872.76±815.21 (p=0.491)
Alpha	0.1v (n=9)	36.85±3.76	30.99±3.18 (p=0.301)	32.05±2.47 (p=0.301)	47.35±12.45 (p=0.470)	78.45±42.76 (p=0.373)	55.74±13.54 (p=0.240)	28.78±3.55 (p=0.204)
	0.5v (n=9)	34.58±3.58	201.92±111.02 (p=0.165)	72.37±33.82 (p=0.314)	29.62±1.99 (p=0.340)	27.31±0.98 (p=0.077)	31.30±2.12 (p=0.505)	29.80±2.15 (p=0.216)
	1v (n=8)	41.60±8.70	740.51±225.10 ***(p=0.015)***	236.59±110.60 (p=0.120)	95.88±57.29 (p=0.389)	80.40±46.79 (p=0.451)	195.22±155.36 (p=0.357)	129.04±65.54 (p=0.234)
	1.5v (n=9)	35.57±2.93	893.70±188.74 ***(p=0.002)***	285.01±71.90 ***(p=0.009)***	203.56±137.16 (p=0.257)	129.77±74.07 (p=0.241)	275.85±137.18 (p=0.118)	129.01±60.07 (p=0.158)
	2v (n=9)	29.19±3.65	1384.76±292.21 ***(p=0.002)***	296.39±86.64 ***(p=0.016)***	77.59±30.94 (p=0.164)	52.69±12.16 ***(p=0.043)***	96.40±48.17 (p=0.184)	97.59±35.10 (p=0.095)
	2.5v (n=8)	28.44±2.07	1221.31±227.54 ***(p=0.002)***	179.75±70.69 (p=0.073)	133.39±41.35 ***(p=0.043)***	120.37±61.93 (p=0.180)	84.11±30.46 (p=0.103)	117.79±53.92 (p=0.142)
	3v (n=5)	186.14±156.62	1889.04±460.18 ***(p=0.018)***	325.63±149.66 (p=0.623)	212.84±129.26 (p=0.905)	95.73±51.97 (p=0.450)	270.70±137.99 (p=0.484)	205.54±109.78 (p=0.848)
	3.5v (n=3)	33.96±6.88	1769.37±362.10 ***(p=0.017)***	176.89±87.46 (p=0.178)	34.29±4.93 (p=0.966)	33.55±2.65 (p=0.959)	84.48±52.17 (p=0.385)	25.86±5.35 (p=0.369)
	4v (n=3)	35.82±7.32	1524.01±340.70 ***(p=0.021)***	166.74±83.00 (p=0.183)	174.21±139.69 (p=0.397)	78.33±19.71 ***(p=0.045)***	30.26±3.08 (p=0.349)	26.02±1.47 (p=0.281)
	4.5v (n=3)	31.43±3.68	1382.72±691.93 (p=0.191)	469.38±245.18 (p=0.211)	146.20±59.44 (p=0.180)	83.58±52.08 (p=0.395)	80.50±54.81 (p=0.519)	25.10±6.76 (p=0.713)
	5v (n=2)	30.92±3.92	1726.20±769.17 (p=0.270)	294.67±170.89 (p=0.359)	34.73±5.77 (p=0.761)	53.50±11.86 (p=0.215)	31.76±5.66 (p=0.715)	111.94±75.88 (p=0.462)

Table D.2. *Continued*

	0.1v (n=9)	42.51±4.06	44.74±4.65 (p=0.578)	46.56±5.39 (p=0.149)	44.03±6.24 (p=0.741)	62.58±17.46 (p=0.227)	49.87±6.84 (p=0.150)	41.14±4.40 (p=0.758)
	0.5v (n=9)	39.98±3.14	94.28±37.23 (p=0.173)	71.66±18.68 (p=0.131)	50.75±6.31 (p=0.059)	51.52±4.28 ***(p=0.026)***	43.02±3.50 (p=0.369)	44.88±5.19 (p=0.214)
	1v (n=8)	48.52±5.08	347.25±95.50 ***(p=0.011)***	134.74±52.58 (p=0.122)	91.84±45.79 (p=0.370)	100.65±48.41 (p=0.313)	143.68±88.28 (p=0.311)	89.51±28.18 (p=0.157)
	1.5v (n=9)	41.55±2.65	502.87±108.91 ***(p=0.003)***	171.80±58.29 (p=0.053)	187.45±126.53 (p=0.277)	111.57±57.15 (p=0.245)	192.46±105.67 (p=0.186)	92.04±28.73 (p=0.097)
Beta	2v (n=9)	39.75±2.24	817.18±153.46 ***(p=0.001)***	134.61±28.65 ***(p=0.013)***	52.20±9.85 (p=0.241)	51.94±2.81 ***(p=0.001)***	72.80±20.63 (p=0.155)	72.88±12.19 ***(p=0.023)***
	2.5v (n=8)	42.34±4.13	731.05±199.08 ***(p=0.014)***	167.22±63.73 (p=0.102)	113.46±37.07 (p=0.111)	86.84±24.82 (p=0.101)	67.49±12.85 (p=0.059)	77.76±17.70 (p=0.053)
	3v (n=5)	75.80±40.27	855.94±203.23 ***(p=0.011)***	179.51±84.28 (p=0.370)	86.72±25.90 (p=0.807)	69.22±17.70 (p=0.801)	104.47±35.77 (p=0.469)	95.66±40.14 (p=0.287)
	3.5v (n=3)	40.77±3.98	667.17±198.73 (p=0.050)	114.46±34.30 (p=0.099)	52.85±6.23 (p=0.166)	47.38±7.70 (p=0.363)	48.69±13.44 (p=0.604)	49.18±5.52 (p=0.250)
	4v (n=3)	39.11±2.88	937.25±292.37 (p=0.054)	107.23±44.79 (p=0.224)	122.30±80.22 (p=0.368)	57.65±12.71 (p=0.203)	44.67±4.04 (p=0.063)	47.35±6.59 (p=0.278)
	4.5v (n=3)	44.22±6.58	1015.44±321.72 (p=0.09)	268.40±144.36 (p=0.25)	116.76±40.41 (p=0.19)	174.40±127.27 (p=0.40)	58.39±27.44 (p=0.54)	38.05±7.76 (p=0.96)
	5v (n=2)	37.43±6.42	952.79±586.53 (p=0.366)	173.41±92.25 (p=0.400)	43.84±4.58 (p=0.664)	39.39±1.87 (p=0.741)	39.50±2.14 (p=0.849)	58.65±21.31 (p=0.584)
	0.1v (n=9)	33.41±1.59	33.25±2.14 (p=0.930)	33.47±1.48 (p=0.965)	39.08±2.81 (p=0.100)	43.18±9.62 (p=0.348)	36.79±3.94 (p=0.437)	35.11±3.16 (p=0.554)
	0.5v (n=9)	38.63±3.09	69.74±14.05 (p=0.073)	61.35±14.93 (p=0.165)	42.37±5.48 (p=0.367)	38.16±3.19 (p=0.885)	35.67±2.53 (p=0.413)	35.82±3.05 (p=0.405)
	1v (n=8)	38.35±4.22	239.92±110.07 (p=0.102)	168.12±103.73 (p=0.242)	187.41±139.04 (p=0.312)	136.75±94.05 (p=0.322)	187.03±144.65 (p=0.331)	100.45±54.42 (p=0.277)
	1.5v (n=9)	37.19±3.37	251.98±65.76 ***(p=0.010)***	183.31±100.61 (p=0.181)	163.49±108.81 (p=0.275)	160.57±110.99 (p=0.295)	181.60±115.06 (p=0.241)	102.53±51.04 (p=0.228)
Gamma	2v (n=9)	44.89±4.80	379.75±69.48 ***(p=0.001)***	90.22±10.37 ***(p=0.003)***	52.15±8.58 (p=0.393)	51.05±3.66 ***(p=0.036)***	62.56±9.31 ***(p=0.032)***	57.66±8.82 (p=0.058)
	2.5v (n=8)	47.06±9.19	393.21±166.36 (p=0.084)	187.00±95.00 (p=0.190)	158.62±69.62 (p=0.155)	123.05±61.79 (p=0.261)	91.90±37.77 (p=0.282)	62.59±10.00 (p=0.126)
	3v (n=5)	98.28±57.88	361.07±91.91 ***(p=0.005)***	133.91±33.43 (p=0.576)	79.65±20.69 (p=0.664)	70.02±10.24 (p=0.590)	76.47±20.60 (p=0.610)	62.60±13.12 (p=0.490)
	3.5v (n=3)	44.32±3.89	315.82±102.01 (p=0.077)	85.06±15.04 (p=0.056)	50.90±3.39 (p=0.299)	49.64±4.31 (p=0.058)	55.28±6.49 (p=0.262)	49.43±2.67 (p=0.390)
	4v (n=3)	41.48±3.58	371.35±84.46 ***(p=0.032)***	78.62±8.80 ***(p=0.022)***	94.21±41.35 (p=0.282)	57.88±8.82 (p=0.187)	52.25±6.65 (p=0.171)	49.95±8.08 (p=0.346)
	4.5v (n=3)	39.38±3.57	567.82±206.41 (p=125)	221.66±121.06 (p=0.263)	109.00±37.51 (p=0.186)	148.89±91.24 (p=341)	70.97±29.06 (p=0.400)	45.28±8.26 (p=0.282)
	5v (n=2)	42.11±0.31	413.38±263.17 (p=0.393)	131.49±29.94 (p=0.208)	49.08±0.67 (p=0.090)	55.20±6.16 (p=0.292)	44.09±0.76 (p=0.318)	54.59±1.61 (p=0.097)

Table D.3. Sample size for each condition in data analysis of contralateral PL following justification.

	PreStim	PostStim-b	PostStim-c	PostStim-d	PostStim-e
0.1v	9	9	8	7	7
0.5v	8	7	7	9	8
1v	8	4	6	5	6
1.5v	7	6	8	8	8
2v	8	5	6	8	8
2.5v	8	4	5	6	9
3v	4	3	3	3	3
3.5v	3	3	2	3	3
4v	3	3	2	2	2
4.5v	2	3	2	2	2
5v	2	2	2	2	2

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Due to the deletion of data points with obvious noise, the sample size for each condition varies.

Table D.4. Sample size for each condition in data analysis of ipsilateral PL following justification.

	PreStim	PostStim-b	PostStim-c	PostStim-d	PostStim-e
0.1v	9	9	8	8	9
0.5v	9	9	9	9	9
1v	9	7	8	8	7
1.5v	9	7	7	6	7
2v	8	6	8	7	7
2.5v	8	6	6	6	6
3v	4	2	5	3	3
3.5v	4	4	4	3	4
4v	4	3	4	4	4
4.5v	3	1	2	1	2
5v	2	2	2	2	1

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Due to the deletion of data points with obvious noise, the sample size for each condition varies.

Table D.5. The effect of SN stimulations on the LFP of contralateral PL in freely moving animal (following justification).

		PreStim	PostStim-b	PostStim-c	PostStim-d	PostStim-e
	0.1v	160.06±5.31	189.62±11.66 ***<u>(p=0.02)</u>***	165.00±12.19 (p=0.563)	160.17±8.95 (p=0.850)	179.79±10.35 (p=0.079)
	0.5v	198.33±23.89	196.73±34.40 (p=0.811)	167.18±11.88 (p=0.078)	215.21±51.93 (p=0.249)	182.60±37.44 (p=0.484)
	1v	177.87±15.05	144.14±18.68 (p=0.170)	279.74±93.93 (p=0.354)	201.75±27.48 (p=0.615)	237.64±40.57 (p=0.364)
	1.5v	216.41±36.12	237.55±40.16 (p=0.983)	255.12±42.26 (p=0.668)	238.96±17.05 (p=0.767)	241.87±32.24 (p=0.642)
Overall	2v	195.95±19.10	300.15±56.58 ***<u>(p=0.041)</u>***	285.17±67.97 (p=0.176)	258.64±37.12 (p=0.332)	269.62±64.02 (p=0.349)
	2.5v	197.10±32.29	360.48±61.95 (p=0.248)	264.46±29.23 (p=0.165)	174.40±15.62 (p=0.968)	319.48±67.25 (p=0.074)
	3v	201.87±27.82	319.65±36.19 (p=0.257)	216.17±49.51 (p=0.792)	324.90±117.26 (p=0.485)	197.33±6.46 (p=0.580)
	3.5v	198.93±44.89	420.30±113.41 (p=0.184)	215.13±33.33 (p=0.050)	211.48±45.03 (p=0.060)	339.85±76.39 (p=0.321)
	4v	189.08±29.81	384.64±144.21 (p=0.338)	281.68±114.61 (p=0.683)	201.30±5.44 (p=0.889)	187.17±32.48 (p=0.969)
	4.5v	162.99±6.43	543.00±189.01 (p=0.501)	243.56±63.40 (p=0.455)	216.41±62.11 (p=0.579)	266.12±90.41 (p=0.48)
	5v	157.76±5.95	512.30±107.82 (p=0.198)	388.02±83.85 (p=0.237)	253.39±110.37 (p=0.562)	226.58±20.12 (p=0.231)
	0.1v	18.26±1.88	34.59±4.70 ***<u>(p=0.012)</u>***	20.70±3.09 (p=0.726)	23.27±4.55 (p=0.547)	33.75±7.51 (p=0.068)
	0.5v	26.42±8.90	33.90±11.22 (p=0.332)	19.98±4.32 (p=0.259)	31.08±9.14 (p=0.795)	27.49±6.20 (p=0.810)
	1v	17.14±1.86	17.86±7.24 (p=0.907)	65.89±34.58 (p=0.230)	47.18±16.21 (p=0.139)	57.42±30.37 (p=0.268)
	1.5v	33.97±7.85	42.38±9.90 (p=0.426)	60.78±20.90 (p=0.266)	56.20±17.62 (p=0.313)	64.18±23.02 (p=0.234)
Delta	2v	36.38±10.52	49.61±14.68 (p=0.182)	54.70±19.68 (p=0.247)	38.00±8.36 (p=0.869)	32.74±4.61 (p=0.848)
	2.5v	28.49±8.89	64.07±15.57 (p=0.182)	50.17±13.54 (p=0.164)	28.23±7.87 (p=0.554)	75.17±21.69 ***<u>(p=0.027)</u>***
	3v	29.89±4.94	57.16±8.37 (p=0.349)	20.03±1.25 (p=0.160)	53.47±22.66 (p=0.520)	30.51±9.87 (p=0.346)
	3.5v	33.74±12.81	86.48±46.18 (p=0.449)	35.20±0.17 (p=0.500)	27.05±6.89 (p=0.435)	112.40±57.34 (p=0.357)
	4v	22.39±5.68	74.02±26.79 (p=0.250)	71.79±57.51 (p=0.601)	29.65±1.04 (p=0.736)	22.58±2.85 (p=0.055)
	4.5v	28.49±2.95	158.61±59.39 (p=0.452)	48.81±10.53 (p=0.227)	41.73±21.83 (p=0.611)	64.28±36.95 (p=0.484)
	5v	24.33±2.81	174.67±61.79 (p=0.258)	109.60±25.39 (p=0.203)	57.05±28.62 (p=0.487)	20.66±5.48 (p=0.400)

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table D.5. *Continued*

	0.1v	44.58±2.81	46.94±7.39 (p=0.690)	40.44±8.81 (p=0.759)	38.29±4.96 (p=0.509)	44.16±4.65 (p=0.897)
	0.5v	55.23±11.43	41.63±7.43 (p=0.095)	40.97±5.33 (p=0.061)	71.40±26.09 (p=0.669)	46.88±12.36 (p=0.397)
	1v	46.45±6.02	27.83±5.35 (p=0.178)	85.71±36.94 (p=0.329)	58.25±10.57 (p=0.405)	62.94±14.18 (p=0.484)
	1.5v	65.36±17.64	70.25±25.30 (p=0.936)	62.72±16.61 (p=0.857)	59.14±9.37 (p=0.495)	66.31±9.71 (p=0.964)
Theta	2v	47.23±7.25	113.71±28.62 ***(p=0.040)***	77.30±26.29 (p=0.211)	59.61±12.52 (p=0.573)	49.59±5.44 (p=0.655)
	2.5v	49.60±10.37	95.31±19.85 (p=0.276)	65.54±14.15 (p=0.417)	36.90±5.45 (p=0.659)	89.98±27.35 (p=0.175)
	3v	50.23±11.97	102.33±14.66 (p=0.334)	54.47±20.34 (p=0.828)	96.00±46.89 (p=0.469)	41.47±4.28 (p=0.716)
	3.5v	40.47±18.48	107.87±36.00 (p=0.123)	40.75±2.81 (p=0.283)	50.45±18.23 (p=0.064)	78.23±34.62 (p=0.509)
	4v	38.79±13.57	124.40±65.02 (p=0.239)	87.74±54.41 (p=0.435)	39.97±7.48 (p=0.414)	37.49±9.14 (p=0.272)
	4.5v	29.31±3.74	183.30±75.57 (p=0.481)	49.48±23.83 (p=0.499)	49.85±11.13 (p=0.220)	65.43±24.27 (p=0.329)
	5v	21.55±1.42	127.17±31.28 (p=0.191)	108.65±57.72 (p=0.380)	58.74±37.02 (p=0.511)	64.27±3.03 (p=0.066)
	0.1v	28.20±1.99	29.98±5.46 (p=0.779)	29.03±1.72 (p=0.184)	26.68±3.17 (p=0.993)	29.41±3.99 (p=0.431)
	0.5v	41.68±8.97	39.12±11.81 (p=0.874)	31.00±2.66 (p=0.503)	34.72±9.35 (p=0.097)	31.17±7.16 (p=0.438)
	1v	38.37±11.50	24.53±2.05 (p=0.263)	40.39±10.97 (p=0.961)	25.89±3.43 (p=0.314)	45.91±14.91 (p=0.455)
	1.5v	45.56±13.38	30.48±3.50 (p=0.266)	41.03±7.07 (p=0.723)	33.35±3.50 (p=0.329)	36.49±2.67 (p=0.587)
Alpha	2v	34.12±5.83	39.62±8.11 (p=0.364)	50.32±15.08 (p=0.237)	49.04±11.45 (p=0.159)	55.79±19.48 (p=0.278)
	2.5v	27.49±3.58	61.40±17.74 (p=0.191)	41.45±8.94 (p=0.238)	25.11±2.58 (p=0.977)	54.55±12.75 (p=0.064)
	3v	36.50±8.22	42.63±2.00 (p=0.863)	55.91±22.01 (p=0.542)	66.25±33.35 (p=0.486)	29.44±2.22 (p=0.550)
	3.5v	35.27±3.07	99.98±45.99 (p=0.314)	39.87±11.62 (p=0.777)	30.88±10.14 (p=0.744)	41.19±8.45 (p=0.633)
	4v	26.12±2.03	66.48±27.65 (p=0.256)	35.17±6.49 (p=0.310)	32.55±12.79 (p=0.614)	43.13±20.29 (p=0.511)
	4.5v	23.96±2.45	77.71±37.80 (p=0.649)	38.70±22.48 (p=0.660)	36.75±18.40 (p=0.650)	49.36±22.16 (p=0.490)
	5v	28.94±2.96	79.63±3.28 ***(p=0.004)***	57.89±11.41 (p=0.181)	36.01±16.05 (p=0.685)	47.65±17.09 (p=0.412)

Table D.5. *Continued*

	0.1v	38.17±1.70	42.98±3.12 (p=0.070)	41.98±2.58 (p=0.138)	38.60±2.05 (p=0.928)	38.75±3.24 (p=0.984)
	0.5v	41.811±1.879	40.94±4.47 (p=0.974)	40.23±2.51 (p=0.893)	39.70±5.70 (p=0.128)	37.74±4.59 (p=0.425)
	1v	44.04±5.27	36.63±3.12 (p=0.133)	43.73±9.36 (p=0.772)	37.28±4.66 (p=0.141)	37.50±4.65 (p=0.232)
	1.5v	36.34±3.67	52.21±4.64 (p=0.161)	44.52±6.46 (p=0.403)	41.86±4.15 (p=0.410)	38.20±4.18 (p=0.683)
Beta	2v	38.83±2.92	47.31±4.14 (p=0.087)	54.89±9.12 (p=0.266)	64.95±13.45 (p=0.169)	85.07±43.62 (p=0.358)
	2.5v	50.03±9.90	66.68±7.95 (p=0.615)	54.00±7.17 (p=0.604)	43.43±3.95 (p=0.808)	48.64±6.53 (p=0.854)
	3v	44.22±7.08	54.22±5.75 (p=0.906)	44.01±7.33 (p=0.437)	55.72±10.20 (p=0.546)	44.09±6.22 (p=0.123)
	3.5v	52.83±10.97	56.82±10.05 (p=0.305)	54.88±10.23 (p=0.145)	57.50±4.84 (p=0.551)	50.58±6.34 (p=0.752)
	4v	50.08±12.89	63.18±18.03 (p=0.683)	45.89±0.76 (p=0.712)	58.99±1.54 (p=0.910)	51.56±7.11 (p=0.898)
	4.5v	41.94±2.46	66.33±15.81 (p=0.649)	59.58±8.71 (p=0.360)	47.43±8.47 (p=0.704)	50.64±10.76 (p=0.630)
	5v	48.18±1.29	54.63±1.22 (p=0.236)	53.51±3.72 (p=0.480)	54.16±16.19 (p=0.757)	52.31±2.84 (p=0.229)
	0.1v	30.86±2.94	35.14±3.48 (p=0.069)	32.85±2.48 ***(p=0.009)***	33.34±3.18 (p=0.191)	33.72±2.75 ***(p=0.005)***
	0.5v	33.19±4.11	41.15±4.80 ***(p=0.039)***	35.00±2.93 (p=0.966)	38.32±4.92 (p=0.712)	39.31±9.20 (p=0.345)
	1v	31.87±3.15	37.29±3.89 ***(p=0.009)***	44.01±8.36 ***(p=0.043)***	27.62±7.05 (p=0.681)	29.03±5.52 (p=0.789)
	1.5v	35.19±4.36	42.23±5.45 (p=0.086)	46.07±6.85 (p=0.095)	48.43±12.75 (p=0.280)	36.70±4.51 (p=0.374)
Gamma	2v	39.39±4.83	49.90±7.95 (p=0.118)	47.96±8.71 (p=0.140)	47.04±9.42 (p=0.999)	46.44±6.69 (p=0.509)
	2.5v	39.96±6.61	62.82±4.15 (p=0.141)	47.96±5.32 ***(p=0.034)***	42.67±3.09 (p=0.144)	54.53±7.33 ***(p=0.002)***
	3v	41.03±4.73	63.31±7.25 (p=0.479)	41.74±3.36 (p=0.923)	53.47±6.85 (p=0.474)	51.82±11.16 (p=0.204)
	3.5v	36.62±5.06	69.14±8.90 (p=0.103)	44.43±14.12 (p=0.355)	45.59±6.81 (p=0.085)	57.46±7.80 ***(p=0.023)***
	4v	51.70±19.87	56.57±11.57 (p=0.846)	41.09±4.56 (p=0.652)	40.13±2.44 (p=0.657)	32.41±1.21 (p=0.563)
	4.5v	39.28±8.21	57.05±11.32 (p=0.505)	46.99±2.16 (p=0.424)	40.64±2.29 (p=0.918)	36.42±3.75 (p=0.637)
	5v	34.75±5.96	76.21±12.69 (p=0.269)	58.38±6.95 ***(p=0.027)***	47.43±12.49 (p=0.617)	41.69±2.64 (p=0.568)

Table D.6. The effect of SN stimulations on the LFP of ipsilateral PL in freely moving animal (following justification).

		PreStim	PostStim-b	PostStim-c	PostStim-d	PostStim-e
	0.1v	189.60±11.30	245.20±58.15 (p=0.413)	197.12±20.35 (p=0.900)	199.08±13.47 (p=0.792)	165.66±8.13 (p=0.172)
	0.5v	192.90±10.27	238.93±42.18 (p=0.288)	188.69±7.95 (p=0.757)	179.88±9.99 (p=0.502)	174.89±4.12 (p=0.144)
	1v	256.20±56.59	181.67±13.04 (p=0.317)	208.94±28.89 (p=0.472)	219.47±37.31 (p=0.565)	223.16±33.84 (p=0.639)
	1.5v	200.23±12.64	368.48±58.42 (p=0.050)	372.69±124.44 (p=0.163)	426.15±117.54 (p=0.088)	283.23±51.50 (p=0.063)
Overall	2v	196.72±18.28	361.62±90.72 (p=0.127)	401.29±74.36 ***<u>(p=0.027)</u>***	410.80±111.90 (p=0.147)	363.02±75.11 (p=0.099)
	2.5v	203.12±20.22	541.60±156.28 (p=0.092)	364.70±143.40 (p=0.273)	402.51±96.54 (p=0.072)	354.81±158.47 (p=0.356)
	3v	178.04±7.22	208.86±13.80 (p=0.334)	553.22±213.23 (p=0.101)	287.33±101.88 (p=0.372)	229.31±55.97 (p=0.424)
	3.5v	193.30±19.89	238.92±28.56 (p=0.131)	207.53±18.10 (p=0.162)	192.38±32.66 (p=0.677)	214.29±47.12 (p=0.614)
	4v	200.89±29.05	248.30±31.63 (p=0.612)	520.97±118.94 (p=0.076)	205.89±15.34 (p=0.853)	218.15±18.63 (p=0.684)
	4.5v	175.73±14.24	286.44	324.57±26.28 (p=0.185)	187.80	212.65±28.59 (p=0.530)
	5v	190.49±25.58	311.57±35.02 (p=0.050)	462.12±201.83 (p=0.366)	222.39±51.90 (p=0.439)	247.74
	0.1v	21.25±3.99	38.17±17.16 (p=0.398)	22.82±4.28 (p=0.990)	23.17±3.16 (p=0.954)	22.31±2.99 (p=0.780)
	0.5v	24.60±4.33	45.23±11.65 ***<u>(p=0.045)</u>***	26.72±2.56 (p=0.669)	23.38±3.54 (p=0.871)	17.53±2.17 (p=0.267)
	1v	51.35±24.23	19.99±5.45 (p=0.320)	23.10±3.65 (p=0.308)	26.82±7.39 (p=0.355)	39.06±16.79 (p=0.677)
	1.5v	28.50±4.43	78.60±21.72 (p=0.076)	127.38±67.48 (p=0.187)	150.10±58.15 (p=0.090)	65.08±23.36 (p=0.153)
Delta	2v	30.07±7.02	100.24±56.46 (p=0.330)	110.94±35.59 (p=0.072)	146.69±68.62 (p=0.171)	77.21±42.71 (p=0.336)
	2.5v	35.37±5.84	59.70±34.65 (p=0.549)	77.50±44.79 (p=0.405)	121.14±58.83 (p=0.189)	58.88±26.65 (p=0.431)
	3v	25.59±5.31	36.56±2.90 (p=0.666)	129.25±40.11 (p=0.167)	62.42±36.90 (p=0.501)	61.17±32.97 (p=0.479)
	3.5v	27.76±2.37	33.48±10.72 (p=0.638)	27.74±4.94 (p=0.996)	32.53±6.42 (p=0.443)	31.67±15.04 (p=0.779)
	4v	36.73±17.83	61.03±27.52 (p=0.775)	149.99±57.25 (p=0.159)	26.71±4.43 (p=0.545)	36.69±8.69 (p=0.999)
	4.5v	32.81±8.86	85.13	89.38±39.14 (p=0.484)	33.26	64.85±23.37 (p=0.554)
	5v	36.58±19.98	51.20±5.69 (p=0.670)	112.12±70.54 (p=0.376)	31.02±14.39 (p=0.501)	63.81

Note: PreStim: pre-stimulation, Stim: stimulation,Poststim: post-stimulation. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding PreStim.

Table D.6. *Continued*

	0.1v	55.59±7.60	76.58±23.94 (p=0.485)	58.58±15.46 (p=0.945)	53.53±5.10 (p=0.405)	38.32±2.78 ***(p=0.047)***
	0.5v	55.09±5.66	70.96±21.53 (p=0.527)	44.97±4.67 (p=0.060)	46.51±6.33 (p=0.288)	46.87±5.99 (p=0.150)
	1v	76.39±27.44	41.58±4.16 (p=0.201)	56.24±11.79 (p=0.458)	54.43±12.01 (p=0.465)	62.43±13.20 (p=0.551)
	1.5v	57.43±7.87	128.80±31.22 (p=0.107)	105.14±52.45 (p=0.308)	134.75±47.75 (p=0.143)	71.35±12.82 (p=0.326)
Theta	2v	52.82±12.46	99.54±25.55 (p=0.101)	134.66±37.00 (p=0.052)	104.04±32.91 (p=0.281)	107.85±28.98 (p=0.168)
	2.5v	47.22±7.13	119.75±73.92 (p=0.399)	113.18±42.87 (p=0.194)	99.17±37.49 (p=0.180)	187.17±140.13 (p=0.368)
	3v	46.80±10.16	42.24±10.37 (p=0.766)	189.00±101.79 (p=0.133)	80.97±43.17 (p=0.422)	55.43±13.27 (p=0.296)
	3.5v	46.49±10.96	67.40±18.55 (p=0.381)	49.23±10.58 (p=0.677)	37.97±10.86 (p=0.789)	58.15±24.04 (p=0.482)
	4v	47.77±4.84	57.50±8.05 (p=0.628)	177.12±64.64 (p=0.148)	52.00±14.36 (p=0.748)	58.14±7.45 (p=0.425)
	4.5v	27.89±5.19	54.79	98.64±6.22 ***(p=0.035)***	55.99	39.37±14.48 (p=0.681)
	5v	43.45±8.41	132.72±41.22 (p=0.224)	201.90±115.14 (p=0.377)	76.02±28.95 (p=0.358)	57.55
	0.1v	36.85±3.76	47.35±12.45 (p=0.470)	35.98±5.59 (p=0.728)	44.88±9.16 (p=0.513)	28.78±3.55 (p=0.204)
	0.5v	34.58±3.58	29.62±1.99 (p=0.340)	27.31±0.98 (p=0.077)	31.30±2.11 (p=0.505)	29.80±2.15 (p=0.216)
	1v	41.60±8.70	26.50±3.37 (p=0.197)	33.97±6.62 (p=0.477)	40.22±12.07 (p=0.869)	32.86±2.79 (p=0.420)
	1.5v	35.57±2.93	53.42±7.75 (p=0.145)	46.38±5.67 ***(p=0.038)***	37.51±9.13 (p=0.776)	46.30±16.65 (p=0.496)
Alpha	2v	29.19±3.65	57.61±15.80 (p=0.055)	52.69±12.16 ***(p=0.043)***	49.03±10.11 (p=0.066)	64.92±14.81 (p=0.057)
	2.5v	28.44±2.07	82.71±35.66 (p=0.193)	51.21±14.56 (p=0.177)	43.27±5.33 ***(p=0.008)***	43.10±12.90 (p=0.310)
	3v	29.56±4.41	36.83±12.79 (p=0.644)	95.72±51.97 (p=0.399)	49.21±20.03 (p=0.349)	33.23±8.15 (p=0.463)
	3.5v	33.95±6.88	34.29±4.93 (p=0.966)	33.55±2.65 (p=0.959)	32.33±2.37 (p=0.910)	25.86±5.35 (p=0.369)
	4v	35.81±7.32	34.63±7.92 (p=0.859)	78.33±19.71 ***(p=0.045)***	30.26±3.08 (p=0.349)	26.02±1.47 (p=0.281)
	4.5v	31.43±3.68	29.71	31.51±1.70 (p=0.417)	25.69	25.10±6.76 (p=0.713)
	5v	30.92±3.92	34.73±5.77 (p=0.761)	53.50±11.86 (p=0.215)	31.75±5.66 (p=0.715)	36.07

Table D.6. *Continued*

	0.1v	42.51±4.06	44.03±6.24 (p=0.741)	45.86±5.70 (p=0.161)	44.08±4.13 (p=0.201)	41.14±4.40 (p=0.758)
	0.5v	39.98±3.14	50.75±6.31 (p=0.059)	51.52±4.28 ***(p=0.026)***	43.02±3.50 (p=0.369)	44.88±5.19 (p=0.214)
	1v	48.52±5.08	44.68±2.91 (p=0.906)	52.81±8.40 (p=0.656)	55.59±6.46 (p=0.152)	47.99±4.55 (p=0.333)
	1.5v	41.55±2.65	57.62±6.64 ***(p=0.015)***	50.40±5.72 (p=0.057)	53.55±6.62 (p=0.090)	53.67±7.39 (p=0.058)
Beta	2v	39.75±2.23	51.26±5.05 (p=0.051)	51.94±2.81 ***(p=0.001)***	52.44±3.84 ***(p=0.028)***	63.44±8.90 ***(p=0.038)***
	2.5v	42.34±4.13	69.77±15.43 (p=0.214)	50.90±5.65 (p=0.075)	50.87±7.38 (p=0.154)	53.26±7.36 (p=0.141)
	3v	35.65±4.03	44.46±1.66 (p=0.090)	69.22±17.70 (p=0.152)	46.64±2.10 (p=0.058)	36.18±1.22 ***(p=0.035)***
	3.5v	40.77±3.98	52.85±6.23 (p=0.166)	47.38±7.70 (p=0.363)	35.94±6.00 (p=0.438)	49.18±5.52 (p=0.250)
	4v	39.11±2.88	42.25±7.45 (p=0.535)	57.65±12.71 (p=0.203)	44.67±4.04 (p=0.063)	47.35±6.59 (p=0.278)
	4.5v	44.22±6.58	47.95	47.19±6.83 (p=0.144)	30.95	38.05±7.76 (p=0.959)
	5v	37.43±6.42	43.84±4.58 (p=0.664)	39.39±1.87 (p=0.741)	39.50±2.14 (p=0.849)	37.34
	0.1v	33.40±1.58	39.08±2.81 (p=0.100)	30.13±4.52 (p=0.424)	29.70±4.24 (p=0.362)	35.11±3.16 (p=0.554)
	0.5v	38.63±3.09	42.36±5.47 (p=0.367)	38.16±3.19 (p=0.885)	35.67±2.53 (p=0.413)	35.82±3.05 (p=0.405)
	1v	38.35±4.22	48.92±7.12 ***(p=0.035)***	42.81±5.17 (p=0.382)	42.41±3.13 (p=0.148)	40.81±5.20 (p=0.095)
	1.5v	37.19±3.37	50.04±1.91 ***(p=0.002)***	43.38±3.48 (p=0.094)	50.25±7.11 (p=0.063)	46.83±4.92 (p=0.066)
Gamma	2v	44.89±4.80	52.97±7.35 (p=0.124)	51.05±3.66 ***(p=0.036)***	58.61±9.74 (p=0.068)	49.59±4.13 (p=0.083)
	2.5v	47.06±9.19	90.17±28.42 (p=0.097)	49.68±7.76 (p=0.183)	46.53±5.13 (p=0.362)	48.23±5.14 (p=0.312)
	3v	40.44±3.08	48.77±6.83 (p=0.759)	70.02±10.24 ***(p=0.034)***	48.09±4.52 (p=0.179)	43.29±3.35 (p=0.794)
	3.5v	44.32±3.89	50.90±3.39 (p=0.299)	49.64±4.31 (p=0.058)	53.61±8.87 (p=0.517)	49.43±2.67 (p=0.390)
	4v	41.48±3.58	52.88±2.06 ***(p=0.047)***	57.88±8.82 (p=0.187)	52.25±6.65 (p=0.171)	49.95±8.08 (p=0.346)
	4.5v	39.38±3.57	68.87	57.85±10.55 (p=0.185)	41.91	45.28±8.26 (p=0.282)
	5v	42.11±0.31	49.07±0.67 (p=0.090)	55.20±6.16 (p=0.292)	44.09±0.76 (p=0.318)	52.98

Appendix E

Results in Table: the Effect of Formalin Injection on the LFP of PL in Freely Moving Animal

Table E.1. The effect of formalin injection on the LFP of PL in freely moving animal.

	B1	B2	0min	5min	10min	15min	20min	25min	30min	35min	40min	45min
Overall	179.33±10.03	254.35±57.14 (p=0.215)	422.67±179.05 (p=0.229)	229.80±29.99 (p=0.158)	294.16±117.88 (p=0.358)	314.33±69.91 (p=0.106)	205.89±21.56 (p=0.381)	188.23±14.46 (p=0.543)	205.87±21.09 (p=0.226)	236.40±47.61 (p=0.223)	293.97±61.27 (p=0.079)	421.88±105.46 (p=0.063)
Delta	21.71±3.33	47.36±14.24 (p=0.132)	156.91±86.84 (p=0.182)	35.90±6.52 (p=0.123)	37.15±13.80 (p=0.300)	58.53±21.41 (p=0.156)	34.27±7.04 (p=0.215)	24.13±7.24 (p=0.624)	27.32±5.96 (p=0.458)	30.23±7.68 (p=0.293)	52.85±17.10 (p=0.079)	79.23±30.79 (p=0.100)
Theta	47.36±5.98	66.96±25.12 (p=0.515)	117.26±53.85 (p=0.273)	70.16±23.20 (p=0.425)	93.01±42.24 (p=0.353)	103.79±30.59 (p=0.135)	55.82±14.09 (p=0.586)	52.30±6.26 (p=0.595)	58.22±8.12 (p=0.424)	64.93±20.37 (p=0.454)	85.84±26.21 (p=0.135)	142.11±46.13 (p=0.079)
Alpha	33.19±4.97	35.49±5.17 (p=0.641)	58.86±26.93 (p=0.350)	38.69±4.28 (p=0.062)	68.93±46.36 (p=0.452)	46.69±8.03 (p=0.238)	33.18±2.69 (p=0.998)	30.38±2.66 (p=0.611)	37.47±5.89 (p=0.450)	37.04±8.35 (p=0.517)	56.11±14.18 (p=0.099)	83.96±17.26 ***(p=0.034)***
Beta	42.01±3.80	48.63±5.18 (p=0.301)	57.40±14.89 (p=0.250)	47.20±10.33 (p=0.555)	53.46±11.04 (p=0.202)	57.89±13.16 (p=0.196)	43.20±3.18 (p=0.808)	42.28±4.71 (p=0.942)	45.72±2.06 (p=0.259)	56.17±11.51 (p=0.226)	50.53±6.02 (p=0.305)	65.69±10.85 (p=0.126)
Gamma	35.05±1.40	55.92±11.67 (p=0.111)	32.24±5.53 (p=0.610)	37.84±6.68 (p=0.645)	41.62±6.14 (p=0.253)	47.44±6.67 (p=0.096)	39.43±2.72 (p=0.231)	39.15±4.34 (p=0.276)	37.12±4.79 (p=0.601)	48.02±5.36 ***(p=0.049)***	48.65±7.79 (p=0.112)	50.91±6.65 (p=0.088)

Note: B1: baseline 1, B2: baseline 2. Values are means ± SE. The bold, italic and underlined data indicate significant difference compared with the corresponding B1.

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Ailing Li earned her B.S. in Biotechnology and M.S. in Environmental Zoology from Lanzhou University, China. Two years after she came to U.S. to purse her Ph.D. degree, she earned another M.S degree in Health and Neuroscience program of Psychology Department at University of Texas at Arlington; and now she is completing her Ph.D. During the past five years at UTA, she started out studying peripheral neurogenic inflammation, and then moved on to investigate the descending inhibitory pain mechanism in the central nervous system. In her dissertation project, she focused on the cortical processing of pain in brain. She investigated how pain influenced the activity in the medial prefrontal cortex. She will continue to study physiological mechanisms of pain after graduation.