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Restored laser evoked potential and decreased gamma band activity in chronic-neuropathic pain patients under dorsal root ganglion stimulation treatment

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Dedicated to my parents

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Abbreviations

IASP	International Association for the Study of Pain
ICD	Classification of Diseases
WHO	World Health Organization
NeuPSIG	Neuropathic Pain Special Interest Group
VAS	Visual analog scale
GRS	Graphic rating scale
NRS	Numeric rating scale
MPQ	McGill Pain Questionnaire
NPQ	Neuropathic Pain Questionnaire
DN4	Douleur-Neuropathiqueen 4 questions
DRG	Dorsal root ganglion
APs	Action potentials
SGCs	Satellite glial cells
ATP	Adenosine triphosphate
PAF	Peripheral afferent fiber
DRGS	Dorsal root ganglion stimulation
SCS	Spinal cord stimulation
EEG	Electroencephalography
ERPs	Event related potentials
BCI	Brain-computer interface
μV	Microvolts
EP	Evoked Potential
LEP	Laser evoked potential
SEP	Somatosensory evoked potential
ms	Millisecond
ECoG	Electrocorticogram

mm	Millimeter
ICA	Independent component analysis
μm	Micrometer
MEG	Magnetoencephalography
S1	Primary somatosensory cortices
S2	Secondary somatosensory cortices
PHN	Post-herpetic neuralgia
CNS	Central nervous system
Na+	Sodium ion
K+	Potassium ion
Ca++	Calcium ion
TNF-α	Tumor Necrosis Factor-Alpha
GDNF	Glial-derived neurotrophic factor
GAP-43	Growth-associated protein-43
BDNF	Brain-derived neurotrophic factor
NT-3	Neurotrophin-3
EFNS	European Federation of Neurological Societies
RCTs	Randomized controlled trials
DBS	Deep brain stimulation
PVG	Periventricular gray matter
CPRS	Complex regional pain syndrome
FBSS	Failed back surgery syndrome
PLP	Phantom limb pain

1. Introduction

1.1 Neuropathic pain and diagnostic criteria

1.1.1 Neuropathic pain

Neuropathic pain is a very severe and intractable disease in clinic because it usually develops in a chronic condition that affects the quality of daily life on the part of patients. In 1994, neuropathic pain was defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (Merskey & Bogduk, 1994) by the International Association for the Study of Pain (IASP). This definition is so broad that many clinicians have found it difficult to classify and examine patients (Jensen et al., 2011). In 2008, this definition was replaced by “Pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system” (Loeser & Treede, 2008). Compared with the 1994 definition, it is more appropriate for the classification of nosology and neurological disorders.

With the deepening of research and ongoing clinical practice, there is an urgent need for more structural and systematic classification of neuropathic pain (Nanna Brix Finnerup et al., 2013). The International Statistical Classification of Diseases (ICD) and Related Health Problems of the World Health Organization (WHO) is the most widely acknowledged disease code and classification (Organization, 2004). Up to now, the ICD 10 is the latest version, which, however, is not suitable for some painful conditions. Therefore, a newer and more precise classification of painful disorders is required. The Classification Committee of the IASP's Neuropathic Pain Special Interest Group (NeuPSIG) has already updated some definitions and content models. According to the latest revised version, it is divided into chronic central neuropathic pain and chronic peripheral neuropathic pain (Scholz et al., 2019). There are 9 common pain conditions

included in this category (Figure 1.1). This model provides one clear diagnostic criterion of neuropathic pain for clinicians and pain-related researchers.

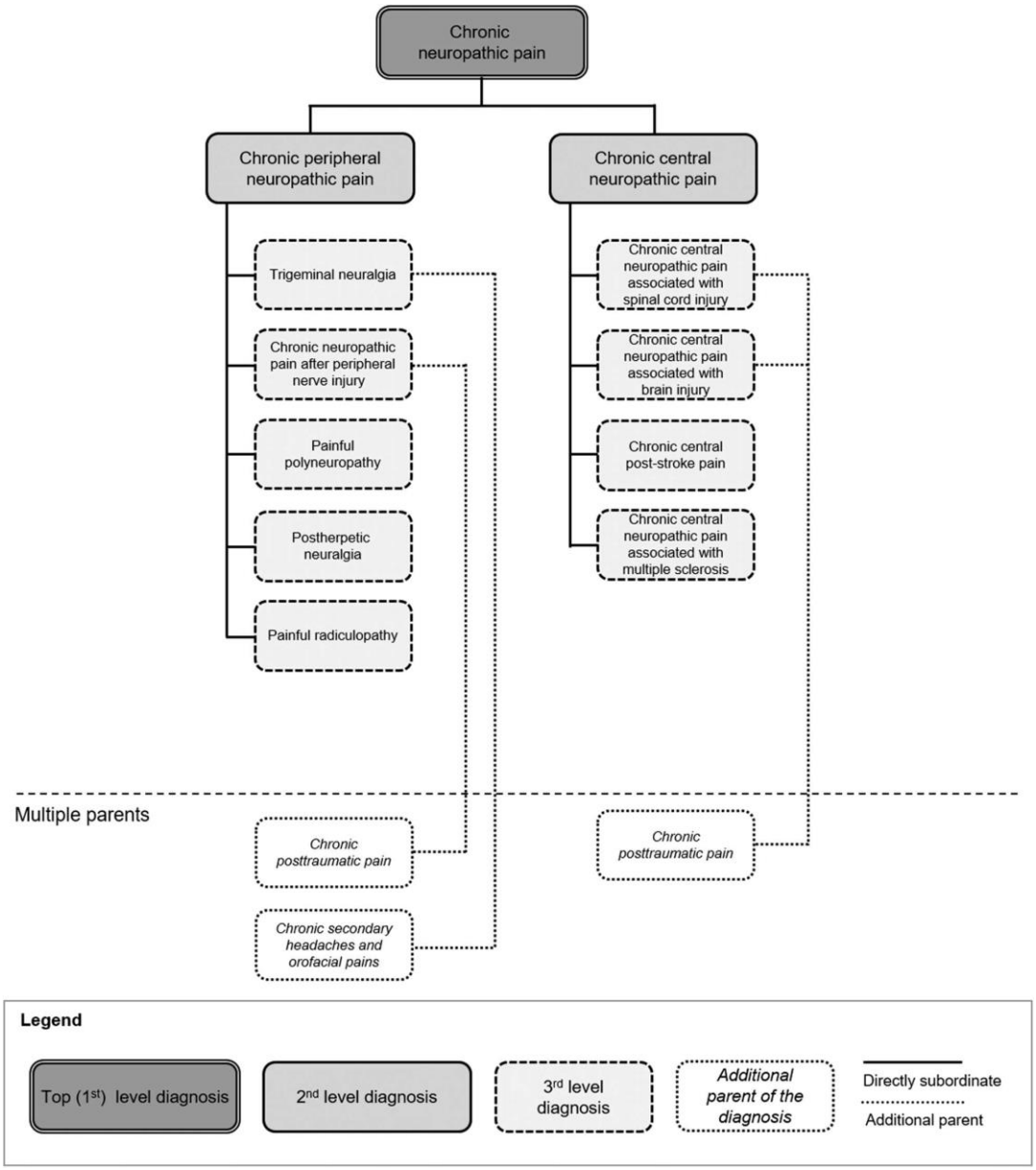

Figure 1. 1 Classification of chronic neuropathic pain in ICD-11 (Scholz et al., 2019).

1.1.2 Diagnosis of chronic-neuropathic pain

Since neuropathic pain was defined in 1994, there has been no effective diagnostic tool used for clearly diagnosing it. According to its definition, nervous system's lesion or

dysfunction is the prerequisite of the diagnosis. Therefore, the medical history of nervous system damage caused by nerve lesion or disease is the symbol characterized by neuropathic pain (G Cruccu et al., 2010). As is well-known, abnormal sensory perception is one of the important clinical symptoms on the part of neuropathic pain patients. The previous research which also revealed the neuronal lesion or disease may damage the central somatosensory pathway. Therefore, all of the factors above should be considered as a basis for diagnosing neuropathic pain.

In 2008, one joint working group of neuropathic pain formulated a grading system for a clinical and research purpose (R-D Treede et al., 2008) by combining the pain history and neurological examination. Based on this grading system, patients can be classified into three categories such as definite, probable, and possible neuropathic pains (R-D Treede et al., 2008). The diagnosis confirmation of the grade is definite and probably needs more future clinical examination. But the grade possibly means the diagnosis of neuropathic pain which is neither confirmed nor excluded. This grade greatly helped the diagnosis of neuropathic pain in clinic at that time. It offers us a personalized diagnostic strategy for private persons. Several years later, an expert panel released an improved grading system (Figure 1.2). In order to better reflect the clinical practice and research, they recommended making some small changes of the grading criteria and adding further annotated terms (Nanna B Finnerup et al., 2016). Meanwhile, this modified grading system also follows the principle of stepwise diagnosis in clinic.

Screening tools are also helpful to diagnosing the patients with potential neuropathic pain. Clinically, many excellent screening tools such as visual analog scale (VAS), graphic rating scale (GRS), numeric rating scale (NRS), McGill Pain Questionnaire (MPQ), Neuropathic Pain Questionnaire (NPQ), Douleur-Neuropathiqueen 4 questions (DN4) and PainDETECT are welcomed by both patients and physicians (Haefeli & Elfering, 2006). These tools serve as the bridge between the definition and the diagnosis

of neuropathic pain. In fact, some tools have already played a role in distinguishing between neuropathic pain and non-neuropathic pain (Bennett et al., 2007). Since these tools are easy to access, patients can even make self-evaluation at home, which is beneficial to recognizing neuropathic pain.

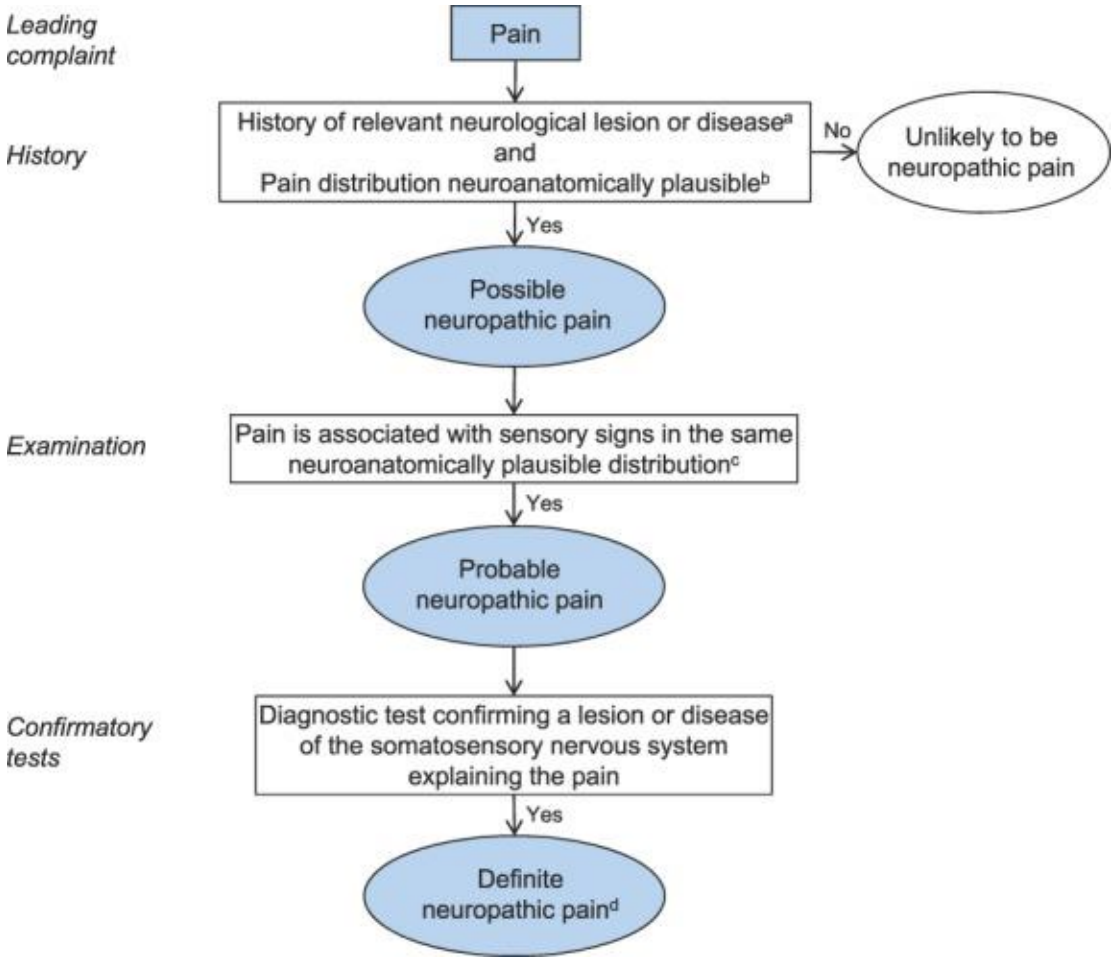

Figure 1. 2 Flow chart of updated grading system for neuropathic pain (Nanna B Finnerup et al., 2016).

1.2 Dorsal root ganglion and dorsal root ganglion stimulation

1.2.1 Anatomical basics of dorsal root ganglion

It is well known that there are 31 paired spinal nerves in the human body, including 8 pairs of cervical nerves, 12 pairs of thoracic nerves, 5 pairs of lumbar nerves, 5 pairs of

sacral nerves, and 1 pair of coccygeal nerves. Each pair of spinal nerves is synthesized by the ventral motor efferent nerve roots and dorsal sensory afferent nerve roots at the intervertebral foramen (Hasegawa, An, & Haughton, 1993). The dorsal sensory nerve roots contain cell bodies of afferent sensory neurons, which form the dorsal root ganglion (DRG). Some researchers have also classified the positions of dorsal root ganglia into three conditions: intraspinal, intra-foraminal, and extraforaminal (Kikuchi, Sato, Konno, & Hasue, 1994). Most of the ganglia are located below the vertebral pedicles and within the neural foramen (Cohen, Wall, Brown, Rydevik, & Garfin, 1990). Under physiological conditions, the stability of the adjacent structure of the intervertebral foramina plays an important role in the maintenance of normal nerve function. The DRG neurons can be divided into A and B different types based on its morphological structure and functions. Type A neurons are larger in size compared with type B neurons, but the ratio of the number of type A neurons to that of type B neurons is approximately 29:71 (Kishi, Tanabe, Schmelzer, & Low, 2002). Type A neurons are primarily responsible for proprioception, while type B neurons are responsible for nociception. This special structure determines DRG's functions in the neural pathway.

Mainly clustered together in dorsal root ganglia, primary sensory neurons are the largest cells in human body, whose length can even reach 1.5 meters (Hogan, 2010). Also known as "afferent neurons" and "receptive neurons," sensory neurons can transmit nerve stimulation from receptive fields or sensory organ to the central nervous system (Aldskogius, Elfvin, & Forsman, 1986). The reason why most DRG neurons are pseudo-unipolar neurons is that the cell body is approximately circular and connected by T-junction with the only axon which is divided into two branches not far from the cell body, with one branch distributing from the body to periphery, and another from the body to the spinal cord. This special structure provides great help for its functions. The T-junction has several functions in the conduction process of action potentials (APs). According to its influence on the conduction of APs from peripheral nociceptor to the

spinal cord, the roles it plays can be divided into the following three aspects: firstly, it acts as an obstacle to prevent the conduction of APs; secondly, it serves as a low pass filter to manage the APs; thirdly, it can actively participate in the conduction of APs (Gemes et al., 2013).

The DRG neurons are surrounded with satellite glial cells (SGCs) which are in charge of the transmission of various neurotropic factors (e.g. bradykinin, cytokines, adenosine triphosphate (ATP). These SGCs are a little different from other glial cells, especially in some specific fields. They may be active in the transmission of biological information from other cells, respond to the signal in their intracellular environment, and influence the DRG neuron cells (Hanani, 2005). It is known that SGCs are also involved after the peripheral afferent fiber (PAF) injury (Rashid, Inoue, Matsumoto, & Ueda, 2004). Therefore, it is likely that SGCs take great responsibility in the processes of neuropathic pain development.

1.2.2 Dorsal root ganglion stimulation

There is a long history of using electrical stimulation in the research field and clinical application. As early as in the ancient Rome, physicians used to treat patients for headaches and arthritis with electric eels. As the research moves on, more and more evidence indicate that the DRG plays an important role in the development and maintenance of neuropathic pain. It is not only passively involved but also actively participates in the pathological process of neuropathic pain. Quickly, the DRG has become one of the research hotspots.

In 1991, rat DRG neurons was regarded as the target to treat pain and inflammation (Bevan & Yeats, 1991). With the development of technology, it is possible to design a system of electrical stimulation for DRG-targeted experiment. These techniques were rapidly applied to the clinic. In 1995, neuromodulation of lumbar 2 dorsal root ganglion

was introduced as a new technique to treat intractable disc pain (Wright & Colliton, 1995). This novel therapy got an exciting outcome at that time. With the average VAS decreasing from 8 to 2.5, many patients returned to work. Henceforth, novel DRG stimulation (DRGS) systems were specially designed and improved. In 2011, the European Union approved the clinical application of DRGS system.

The first feasibility study of DRGS was jointly designed and implemented by four clinical centers in 2012 (Deer, Grigsby, Weiner, Wilcosky, & Kramer, 2013). This study enrolled ten chronic intractable pain patients. All the participants were dissatisfied with the pain relief of current treatments (i.e. medication, interventional treatment or surgical intervention). The leads were implanted in the lateral epidural space close to the dorsal root ganglion. Electrical stimulation was provided by the outside additional generator system which is connected with the leads. After the stimulation system was activated, all patients experienced regional pain relief. At the end of the trial, the pain was reduced by 70% on average compared with baseline. Meanwhile, there was a 78% reduction of analgesic intake in patients. During the whole experiment period, none of the device-related adverse event was reported to have confirmed the safety of this system. Compared with traditional spinal cord stimulation (SCS), DRGS looks more suitable for the treatment of low back pain. It can specifically target this anatomical region, which is difficult for SCS to achieve. The excellent results of this study will greatly promote the development of related research in the future.

In 2013, another significant article on DRGS was published (Liem et al., 2013). The article first reported the application of fully implantable DRGS device in chronic pain patients. Meanwhile, the researchers carefully evaluated the performance of this new system under several focal nerve-related pain conditions during different experimental periods. There are thirty-two subjects included in this study. After six months' therapy of DRGS, the average pain ratings reduced by 58% compared with the baseline. The

pain scores in different anatomical regions including the back, legs and feet decreased by 58.1%, 69.3%, and 84.5%, respectively. Interestingly, when the stage of DRGS was over, the pain ratings rapidly increased to nearly the baseline level. In addition, the paresthesia map also shows that paresthesia intensity does not change with body position. The results of this prospective study have fully demonstrated that due to the high selectivity of DRGS, it can be used in the treatment of pain regions where traditional SCS are difficult to cover.

Clinically, the management of neuropathic pain in the groin region is difficult, especially after inguinal hernia repair surgery (Eklund, Montgomery, Bergkvist, & Rudberg, 2010). It is estimated that about 7-20% of all patients suffer pain after surgical operations and about 31% are under neuropathic pain conditions (Haroutiunian, Nikolajsen, Finnerup, & Jensen, 2013). As a novel technique, SCS is also applied to the treatment of groin pain (Elias, 2000; Yakovlev et al., 2010). One of the biggest problems concerning SCS therapy is the inadequate coverage of the pain areas, leading to paresthesia in non-pain areas. DRGS therapy can perfectly overcome these shortcomings. A retrospective study reported a group of 25 neuropathic groin pain patients who received DRGS therapies (Schu et al., 2015). The average pain ratings decreased by 71.4 ± 5.6%. Another long-term prospective study including 34 neuropathic groin pain patients with DRGS therapy also attained a satisfying outcome (Morgalla, Bolat, Fortunato, Lepski, & Chander, 2017). After three years follow-up, the average VAS of patients dropped from 8 to 4.5. These pieces of evidence have demonstrated that DRGS can provide an excellent pain relief for patients with neuropathic groin pain.

1.3 Basics of electroencephalography recording

Electroencephalography (EEG) is a technique for recording the spontaneous, rhythmic and weak bioelectrical currents of brain cell populations. In 1924, the first human

electroencephalogram was successfully recorded by Hans Berger. Since then, as a convenient and non-invasive method, the EEG recording technique has been rapidly applied to the clinic and constantly improved. As a result, it has been successfully and typically used in the diagnosis of epileptic seizures, hemicrania and psychiatric disorders. Additionally, EEG has also been widely applied to research fields such as event related potentials (ERPs), cognitive neuroscience, psychophysiological research, and brain-computer interface (BCI).

In 1957, Jasper et al. first reported the standardized system of electrodes placement (Jasper, 1958). This system is also known as the International 10-20 system (Figure 1.3). The placement of the electrodes is based on the percentage of scalp distance between the four important landmarks (the nasion, the inion, the left and right preauricular points) of the skull. The brain regions are proportionally divided into several parts, which are represented by the different electrode names. The frontal, central, temporal, posterior and occipital regions are labeled with different electrode letters F, C, T, P, and O, respectively (Klem, Lüders, Jasper, & Elger, 1999). The numbered electrodes on the left side of the head are represented by odd numbers while those on the right side of the head are by even numbers. This traditional system has also become the most widely used system all over the world. In order to get a more detailed EEG, a higher resolution system was developed (Chatrian, Lettich, & Nelson, 1985) based on 10-20 electrode system. It expanded the electrode numbers to 72, which became the standard system of clinical EEG recording (Nuwer et al., 1998). In some research fields, the EEG acquisition systems with 128 channels and even 256 channels are available (Oostenveld & Praamstra, 2001; Suarez, Viegas, Adjouadi, & Barreto, 2000).

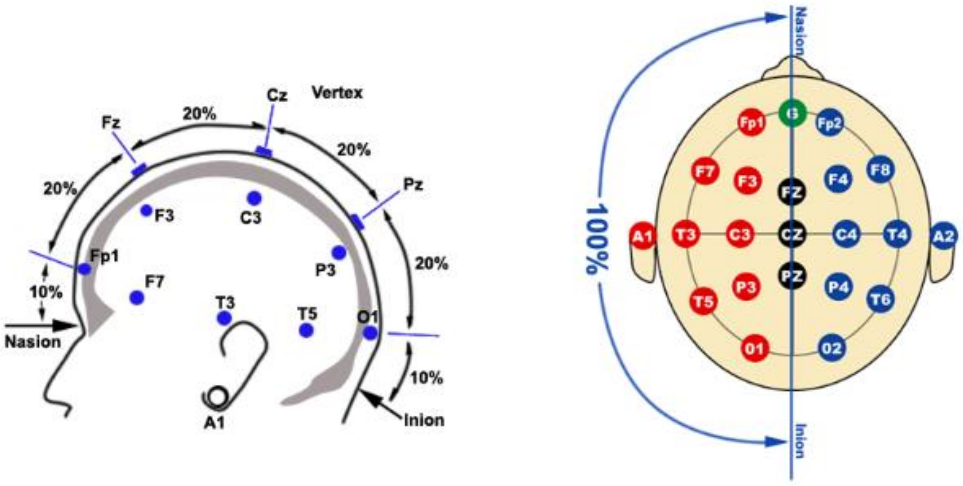

Figure 1. 3 Sketch map of standard electrodes placements of the International 10-20 system (modified from The McGill Physiology Virtual Lab (Lab, Access data Feburary 04, 2020))

The human brain contains about 100 billion neurons (Herculano-Houzel, 2009). The weak electrical activity of these cells constitutes the basis of local current flow. Generally, the recorded scalp EEG signal can reflect the electrical activity and functional status of the brain (Shaker, 2006), which can be rendered by waveforms. The brain waveform contains a lot of important information such as frequency, amplitude, and phase. The amplitude of the EEG signal is quite small, which is measured in microvolts (μV) from peak to peak. The normal value ranges from 0.5 to 100 μV (Teplan, 2002). Regarding frequency, it is usually classified into several groups, such as delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-100 Hz)(Miller, 2007; Saby & Marshall, 2012). Alpha waves are the major rhythm waves of normal adults when their eyes are closed and relaxed (Ergenoglu et al., 2004). They can be found in the posterior and occipital regions and are the most studied human brain rhythm. Beta waves are also considered as normal rhythms in healthy subjects, which can usually be observed in frontal and parietal lobes when the eyes are open (Kumar &

Bhuvaneswari, 2012). This rhythm is strongly related to the mental states of the person. Its activity may be increased by many drugs such as benzodiazepines and barbiturates (Rangaswamy et al., 2002). In patients with brain injury, a prominent decrease in beta rhythm is clearly observed (Tebano et al., 1988).

1.4 Laser evoked potentials

Also known as Evoked Response, Evoked Potential (EP), which means an electrical potential response, can be detected at the special part of the brain when a specific stimulus is given to the nervous system (from the receptor to the cerebral cortex). The EP record is the reflection of the nervous system to the stimulus itself, which means it reflects the special electrophysiological process of the brain to the stimulus. It is different from the spontaneous potentials of the brain. The EP can be detected by EEG and other electrophysiologic recording methods. The laser evoked potential (LEP) is one subtype of the evoked potentials. In fact, it is the response of the brain to laser-generated radiant heat pulses. The nociceptive and thermo-receptive nociceptor can be specially activated by the laser pulses before being reflected in the cerebral cortex. This technique has been employed in many studies regarding the diseases of peripheral and central nervous system (Garcia-Larrea et al., 2002; Truini et al., 2003).

In 1976, Carmon et al. first introduced the application of LEP in humans (Carmon, Mor, & Goldberg, 1976). Four healthy volunteers were enrolled in this study. The CO_2 laser was employed to induce brief pulses of painful sensations. Four electrodes (Cz, C3, C4, P3) were placed separately on the surface of scalp for the EEG recording. According to the results, a late negative-positive component can be detected only from the vertex when the two following conditions are satisfied at the same time. The first is the noxious laser beam stimulus, and the second is the subjects that can experience the actual pain. Interestingly, the amplitude of the response was related to the individual sensation. Meanwhile, they also found that there is a relationship between the

component's latency and stimulus intensity. In 1978, another study aimed at exploring the relationships between LEP parameters and other conditions such as stimulus intensity (Carmon, Dotan, & Sarne, 1978). A series of experiments were systematically conducted to explore the potential relationship between evoked response and stimulus intensity. The results indicated a linear relationship: the amplitude of the evoked response increases as the magnitude of the subjective sensation increases. That is to say, LEP can reflect the sensory function and evaluate the sensation process. Therefore, LEP can be one appropriate objective tool for pain assessment.

Since LEP was developed as an efficient tool for pain research, many researchers have focused on this promising field. With the research progresses, the components of LEP were gradually revealed. In 1980, Kenton et al. observed that the late components of somatosensory evoked potential (SEP) are related to the first acute pain after the CO_2 stimulation (Kenton et al., 1980). In 1987, Bromm et al. published their research results about late and ultra-late components of pain-related-and-evoked potentials (Bromm & Treede, 1987). They employed the high-power CO_2 laser stimulator with a wavelength of 10.6 μm. The EEG was continuously recorded as usual. The results showed that there was a vertex of negativity at 235ms followed by a vertex of positivity at 380ms after the laser stimulation. At about 1300 ms, the amplitude of the delayed vertex of positivity can reach 8μV. Compared to the results of previous studies, these two waveforms were named N240-P370 components and N1050/P1250 components. In fact, the appearance of the late components N240-P370 represents the activation of the A-δ fiber pathway, which is characterized by rapid and stinging pain, while the ultra-late components N1050-P1250 represent the activation of the C fiber pathway, which is characterized by slow and dull pain. In 1989, Kakigi et al. reported several other components of the LEP (Kakigi, Shibasaki, & Ikeda, 1989). They observed a complex of negative-positive-negative waves after the laser stimulation of the hand and named it N200-P320-N500. Evidence has also proved that the P320 is the most stable potential,

which has a largest waveform. In addition, the voltage amplitude of P320 is positively correlated with the stimulus intensity. Besides, another study reported the results of electrical stimulation and CO_2 laser stimulation to activate brain-evoked potential components of A-β and A-δ fibers, respectively (Kunde & Treede, 1993). The N110 component induced by electrical stimulation is similar in appearance to the N170 component caused by CO_2 laser stimulation. The evidence suggests that these components are all the results of activation of secondary somatosensory cortex.

According to these studies, several LEP components were gradually becoming clear: N1 was a negative wave with a latency of about 170 ms, N2 was also a negative wave with a latency of about 240 ms, and P2, also named P400, was a positive wave with a latency of about 400 ms (Siedenberg & Treede, 1996). In clinical practice, the representative negative-positive wave complex N2-P2 is the most studied component. The maximum amplitude (peak to peak amplitude) of this complex can be measured at the vertex (Bromm & Lorenz, 1998). As was reported, the second somatosensory area of the brain may be the origin area of the N1 component, while the insular cortex of brain may be the origin area of the N2 and P2 components, and the anterior cingulate cortex may also be the origin area of the N2 component (Frot, Rambaud, Guénot, & Mauguière, 1999; Garcia-Larrea, Frot, & Valeriani, 2003). Compared with healthy subjects, the LEP of patients with neuropathic pain showed smaller amplitude, suggesting that there may be dysfunction or damage in the nociceptive system (Romaniello, Cruccu, Frisardi, Arendt-Nielsen, & Svensson, 2003).

1.5 Gamma band activities of the brain

The field of signal analysis of EEG has always been a very difficult field of research. Human EEG represents spontaneous and non-paroxysmal signals (Bhattacharya, 2000), which represent complex brain activity. However, these electrical activities are closely correlated with various sensory processing and multiple information integration (Gross,

Schnitzler, Timmermann, & Ploner, 2007). Over the past decades, the traditional EEG research has aimed at two different directions which are time domain and frequency domain. Although these two methods helped researchers reveal a lot of knowledge about the brain, our understanding about its information processing mechanism is still not comprehensive. The ERP study plays an important role in the field of cognitive neuroscience. Most of the analytical theories focus on the peaks induced by the events themselves or the changes in the EEG power spectrum. Although some neurophysiological mechanisms are revealed, these analyses of raw EEG data neither completely model the event-related dynamics nor isolate the signals of associated cerebral cortex regions which are contributing (Makeig, Debener, Onton, & Delorme, 2004). Nevertheless, the EEG data contains important information about neural oscillations and their synchronizations, which gives us an opportunity to explain the underlying neurophysiological mechanisms about the oscillation in vivo human studies (Roach & Mathalon, 2008).

For a long period of time, several methods of analyzing the EEG data have been used. Band power spectral analysis is one of the common methods. Many studies have shown that there is a strong relationship between frequency bands (i.e. alpha, beta, and gamma) and various pain conditions. Under experimental conditions, painful stimuli can activate the brain network, and cause the neuro-physiological changes in somatosensory and prefrontal cortices systems (Tracey & Mantyh, 2007). This method was successfully applied to the field of auditory, vision and mental disease research (S. Li, Hong, Gao, Wang, & Gao, 2011; Makeig et al., 2002; Roach & Mathalon, 2008). As for pain researches, most of them are about traditional ERP studies, and related research on frequency band activity analysis is still insufficient. For this reason, we have employed this EEG spectral analysis method and explored the changes of gamma band activity in neuropathic pain patients under DRGS treatment.

Recent researches on EEG band activity have also indicated that gamma band activities are closely related to transient pain stimuli. In animal experiments, the authors have shown that the gamma band power of rats with chronic inflammatory pain is significantly increased by electrocorticogram (ECoG) recording (Wang, Xing, Li, & Wan, 2016). In human experiments, it has also been found that gamma oscillations in the central region can be activated by painful stimuli (Tiemann, Schulz, Gross, & Ploner, 2010). In addition, another study showed that gamma-band activity is strongly related to the intensity of painful stimuli (Hu, Xiao, Zhang, Mouraux, & Iannetti, 2014).

It has been reported that these findings were all based on healthy volunteer experiments, but for chronic neuropathic pain, it was a more complex and severe condition. The possible mechanism of chronic neuropathic pain may be different from acute pain, which also increased the difficulty of chronic neuropathic pain research. A recent study has shown that the gamma oscillations induced by tonic heat stimuli participate in the process of ongoing pain (Schulz et al., 2015). Meanwhile, another study has also proved the enhancement of gamma oscillations in tonic muscle pain processing (L. Li et al., 2016). Compared with healthy volunteers, the gamma band activity in patients with neuropathic pain showed a significant enhancement (Lim, Kim, Kim, & Chung, 2016). All the related evidence has shown that the activities of gamma band are involved not only in acute pain processing but also in chronic pain processing.

1.6 Aims of the study

It is well known that dorsal root ganglion is an important part of pain pathways and plays a critical role in pain processing (Devor, 1999). Naturally, it is considered as one of the therapeutic targets. DRGS treatment has been reported to provide pain relief in various chronic neuropathic pain status(Deer et al., 2019). LEP is a reliable, objective marker of pain processing (Bromm & Treede, 1984) and grade A recommendation for assessment of pain pathways (Haanpää et al., 2011). Our group’s previous study has

already shown that LEP can be restored to normal values by using DRGS therapy in patients with local neuropathic pain (Morgalla et al., 2019). Band power spectrum analysis is one of the useful methods of cognitive neuroscience, which can provide us with integrated neurophysiological processing information (Saby & Marshall, 2012). The gamma band power in neuropathic pain patients are enhanced (Lim et al., 2016; Zhou et al., 2018). Although this method has been applied, its use in pain research is still insufficient.

Therefore, we employ LEP and EEG gamma band power spectral analysis to explore the underlying mechanisms of chronic neuropathic pain under the DRGS therapy. We are interested in whether the DRGS induced recovery of LEP has a transient or a lasting effect and the timeliness of the voltage amplitude is restored to relative normal values and whether the DRGS induces changes in gamma band power. The protocol of EEG recording for LEP on healthy volunteers has been established (Figure 1.4).

Hypothesis 1: The LEP amplitude restores in a few days after activating DRGS therapy in chronic neuropathic patients.

Hypothesis 2: The DRGS has a lasting effect rather than a transitory effect on chronic neuropathic pain patients.

Hypothesis 3: The power of gamma band decreases in a few days after activating DRGS therapy in chronic neuropathic patients.

Hypothesis 4: The change in power of gamma band is correlated with NRS.

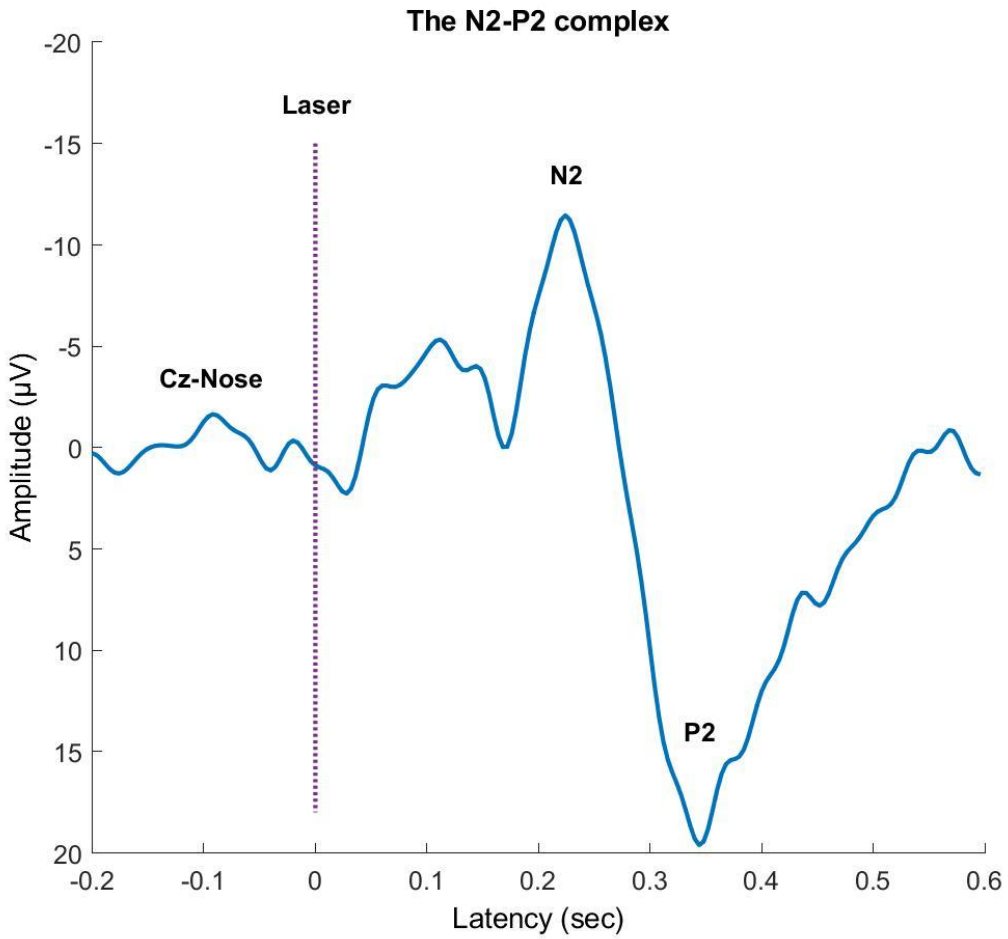

Figure 1. 4 The N2-P2 complex components of LEP in one healthy volunteer

2. Material and Methods

2.1 Study description

This is one prospective, open-label and non-placebo controlled study. The experiment has been conducted in a special modified room allowing the use of a laser system. During the whole experiment, all participants wear the laser goggles. Eligible and screened patients sit on reclining armchairs. The patient wears EEG caps suitable for the head circumference and connected to the EEG recording system. All patients are told to keep their eyes open and their body stable. Three different regions of the body are selected as experimental areas, in which the chronic neuropathic pain area of one limb is used as the experimental area, the corresponding area of the other limb without pain is the control area, and the test area is adjacent to the control area. The test area is used to obtain LEP to verify the setup. We have recorded the results under two conditions: DRGS system switched ON and OFF. Every measurement consists of 5 blocks. The patient reports the NRS of the region of neuropathic pain before the start of the experiment. At the end of each block, the patient reports the average NRS of perceived evoked pain. We performed the assessment of the patients for seven days at three different time points (day1, day4, and day7) after the whole DRGS system was implanted. During this period, medication remained the same.

2.2 Participants

A total of 9 patients (age 56.78±12.80, range 36-77 years old, 2 females and 7 males) participated in this experiment (Table 2.1). These patients suffer chronic unilateral localized neuropathic pain in the groin or knee region. All the enrolled patients come from the pain clinic at the department of neurosurgery of the Eberhard-Karls University in Tuebingen, Germany. We have designed a series of strict criteria to recruit patients. More detailed information is as follows:

2.2.1 Inclusion criteria:

1. Between 18 and 80 years of age
2. Confirmed diagnosis with chronic neuropathic pain affecting one lower limb (including groin or knee)
3. Confirmed the lesion of peripheral nerve root
4. Received formal and systematic medication treatment for more than 6 months, unsatisfied efficacy or the existence of drug-resistance
5. Willing to take part in the study and understand the terms of the informed consent

2.2.2 Exclusion criteria

1. Widespread nociceptive pain
2. Traumatic brain injury
3. History of psychiatric issues or disorders (e.g. severe emotional and mental conditions)
4. Skin lesion or disease in laser-stimulated regions

Table 2. 1 Demographic details of the 9 neuropathic pain patients

No.	Sex	Age (years)	Location of Pain	DRG levels of stimulation
01	Male	52	Left groin	L1&L2 Left
02	Male	50	Left groin	L1&L2 Left
03	Male	67	Left knee	L3&L4 Left
04	Male	36	Right groin	L1&L2 Right
05	Male	46	Right groin	L1&L2 Right
06	Male	53	Left groin	L1&L2 Left
07	Female	61	Right knee	L3&L4 Right
08	Female	77	Left knee	L3&L4 Left
09	Male	69	Left knee	L3&L4 Left

2.2.3 Enrollment and ethics

The study (Nr. 096/2011BO2) was approved by the ethics committee of the University of Tuebingen. All enrolled participants were required to explain detailed details of the experiment before signing informed consent. This is an experiment without additional financial compensation, so we have encouraged the participants to complete all experiments, but they can choose to opt out freely at any time without any formal explanation.

2.3 Experimental design

2.3.1 Preparation before experiment

The first experiment was always performed in the morning one day after the whole DRGS system was implanted. The laboratory was specially transformed for the using of laser device. Laser safety protection complies with German national standards. The room temperature was controlled at about 22℃. The patient was asked to sit in a comfortable reclining armchair after arriving at the laboratory. Before the experiment, the patient was carefully informed of the experiment procedure and relevant announcements. Then the patient was required to indicate the area where he/she felt the most painful. This area was marked with a marker and used as the affected area. The contralateral homologous area was used as control area at the same time. Besides, another small area on the contralateral non-painful limb near the knee corresponding to the unaffected dermatome was marked as the test area. These three areas were the stimulation areas necessary for the experiment. During the whole experiment, the position and range of these three areas were fixed and remained the same.

2.3.2 Nociceptive laser stimulation

We employed a CO_2 laser device (MCO25 plus, KLSMartin, Tuttlingen, Germany) (Figure 2.1). The beam diameter and pulse duration were set at 3.5 mm and 15 ms, respectively. Based on our experience, these fixed parameters of the laser are the optimum to cause a pinprick sensation and will not burn the skin at the same time. The laser beam was delivered on the skin region corresponding to the selected dermatome to activate afferent nociceptors. Protective goggles were used during the whole experiment.

Figure 2. 1 CO_2 laser device (MCO25 plus, KLSMartin, Tuttlingen, Germany)

Prior to the formal experiment, we first detected the patient's pain threshold. This step was performed in the test area which was described above. Since our patients have unilateral neuropathic pain, we determine the pain thresholds in the test area. In order to ensure the accuracy of the measurement, we do not switch ON the DRGS system after the whole DRGS system implantation. Before testing the laser stimulus, the patient was told that the pain caused by the laser should be sharp, unpleasant but tolerable, and felt like drop of boiling water splashing on the skin. This degree of pain is roughly equivalent to the level of which NRS is 4. Besides, we also told the patient not to move the body and try to stay stable as much as possible. Three transient and continuous laser pulses were delivered to the skin surface with an angle of 90° to ensure that the nociceptor would be activated with the minimal energy. After that, the patient was asked to report the degree of pain sensation according to NRS from 0 – 10. The intensity of the laser pulse always started at a low level before increasing on a small scale according to the patient's pain assessment results. When the patient reported the painful sensation was like what he/she had been told before, we recorded the value of laser power and set it as a fixed parameter during all subsequent experiments.

Since the laser device was accompanied by click sound when emitting the laser beam, in order to eliminate the auditory evoked potentials that may be caused by such noise interference, we used in-ear headphones to play recorded click sounds to suppress this potential irrelevant effect. We gradually increased the volume till the patient could not hear the sound from the actual laser click. The volume setting remained the same until the end of the trial.

The formal measurement always started from the control area after the individual pain threshold was confirmed. The size and location of this area was similar to the pain area on the opposite side. Two conditions were applied in this section: DRGS switch OFF and ON. We usually started from the OFF status. The stimulation consisted of 25 to 30 laser shots per section. The patient was also told to count the number of times they would feel a painful laser shot. In order to avoid the habituation of the nociceptors and the overheating of skin, we slightly moved the stimuli position after each release of the laser. Meanwhile, the patient's pain perception elicited by the laser during this section was maintained and the equivalent of NRS was 4. After that, we shifted to the affected area. The experimental procedure was the same as in the previous control area. When these two blocks were completed, we switched on the DRGS system. Next, there was a 15 minutes break for the patient. We repeated the experimental blocks from the control area to the affected area. After the completion of experiment, the DRGS system always remained ON status. This measurement was marked as the first experiment (day 1). At fourth (day 4) and seventh day (day 7) after the first experiment, we repeated the same experimental procedure with DRGS system ON.

2.3.3 Electrophysiological measures

We employed the 32-Channel EEG system (LiveAmp and actiCAP, Brain Products, Gliching, Germany) (Figure 2.2) for the EEG recording. The hardware system mainly consists of 32 active Ag/AgCl electrodes, matched caps, cables and special EEG

amplifier. As for software, we utilized the matched workstation (Brain Recorder version 2.0, BrainProducts, Gilching, Germany).

Figure 2. 2 The active Ag/AgCl electrodes and cap of 32-channel EEG system

Firstly, we set up the EEG system hardware according to the user manual. Secondly, we used a measuring tape to measure the patient's head circumference. The measurement ranges from the glabella to the occipital protuberance. At the same time, we confirmed the position of Cz electrode in accordance with the International 10-20 system. Thirdly, we selected the corresponding electrode cap for the patient according to the head circumference. Thereafter, we connected the EEG electrodes to the electrode cap of the patient. In addition, one electrode was attached on the nose as the reference electrode, and another two electrodes were employed for recording eye movements. The impedance of all electrodes was kept below 5 kΩ. During the EEG recording, electrophysiological signals were amplified and digitized. The average sampling rate was 1,000 Hz.

The patient was asked to keep her/his eyes open, looking forward and avoiding blinking as much as possible. We also set a fixed point on the wall to allow the patient to fix the

viewing angle. In order to ensure that the patient is paying attention to the experiment, the patients were asked to count the number of painful laser stimuli and report them after each block.

2.3.4 Pain measurement

We used the NRS to assess the patient's pain intensity during the experiment. The numbers ranging from 0 to 10 represent the different intensities of pain; with 0 indicating no pain and 10 is the worst possible pain condition. The patient was required to mark the number that best matches his/her pain condition. A total of four pain assessments were conducted. The first two assessments were performed at different time points on the first day (day 1) of the experiment. The first one was mainly used to understand the pain condition before he/she receives the DRGS therapy. The second one was executed after we switched ON the DRGS system. It was the immediate reflection of short-term effect after the treatment. The third and fourth assessments were carried out respectively on the fourth day (day 4) and seventh day (day 7) measurement under the ON status of DRGS system.

2.4 Data processing

The EEG data were stored in the hard disk of the data acquisition workstation. We used the open source toolbox EEGLAB (v14.1.1, Swartz Center for Computational Neuroscience, San Diego, U.S.A.) (Delorme & Makeig, 2004) and Letswave (v7.0, Institute of Neuroscience, Université catholique de Louvain, Belgium) running on MATLAB software (R2017b, MathWorks, Massachusetts, U.S.A.) to do the off-line analysis. Two separate analyses were performed to obtain LEP and gamma band power spectral density.

For LEP processing, at first, we performed the pre-processing steps of the EEG raw data. The continuous EEG data were down sampled from 1000 Hz to 250 Hz. The nose

electrode was selected as the reference electrode. Then a band-pass filter between 0.5 and 30 Hz was applied to the data. Subsequently, the EEG data was segmented into epochs ranging from -200 ms to 600 ms and time-locked relative to the laser stimulus onset. The reference interval of baseline correction was set between -200 ms and 0. Because eye movements or blinks were included in the epochs, we applied two methods in sequence to reject these ocular artifacts. The first method was to implement automatic rejection of extreme values through. The effective interval of threshold was set between -50 μV and +50 μV on electrode Cz. The amplitudes exceeding this range were considered as artifacts and eliminated. After automatic rejection, a second method was applied to perform the manual rejection by visual inspection. The epochs containing artifacts were selected upon inspection for removal.

After completing these processes, we computed the average waveform for each block. As was reported, the maximum amplitude of widespread negative-positive wave complex (N2-P2) can be detected at the vertex (Bromm & Lorenz, 1998). Hence, we selected the Cz electrode to perform the subsequent analysis. According to the features of latency, amplitude, and scalp distribution, the N2-P2 wave complex was defined. After the onset of laser stimulation, the most negative peak and the most positive peak within the time intervals from 150 ms to 260 ms and from 260 ms to 500 ms were defined as N2, and P2, respectively. In some trials, LEP was not detected in the affected area due to the neuropathic pain, so we estimated the N2 and P2 amplitude according to the latency data of the contralateral control area, which served as the reference for the analysis. Some important features such as the latency period and amplitude were all measured and recorded for the subsequent statistical analysis.

To compute gamma band power, we performed the pre-processing steps of the EEG raw data. First, channel locations were confirmed according to the 10-20 EEG system. The sampling rate of continuous EEG data was 1000 Hz. Then the data was band-pass

filtered between 0.5 and 100 Hz. Subsequently, the independent component analysis (ICA) method was employed to remove the artifacts such as eye movements and muscle activity. Then the EEG data were segmented into epochs ranging from -5000 ms to 0 ms and time-locked with the laser stimulus onset. These epochs reflect the resting state EEG without contamination from the previous LEP.

After these pre-processing steps were completed, we calculated the band power by using Welch's method. Our goal was to calculate the power of the gamma band, so we chose the EEG frequency band from 30 Hz to 100 Hz for estimation of gamma band power. To avoid artifacts from the power line at 50 Hz used for operating the laser, the band ranging from 45 Hz to 55 Hz was removed. Therefore, the gamma band was divided into two distinct parts: the lower gamma band (30-45 Hz) and the higher gamma band (55-95 Hz). The power was also calculated independently. The statistical electrode is C3 or C4, which depends on the physiological contralateral side of the patient's painful limb. The numerical value of average power was also measured for later statistical analysis.

2.5 Statistical analyses

We employed the SPSS (v25.0, IBM, Armonk, U.S.A.) software to perform the statistical analyses. For the LEP data and NRS data, we first examined whether it was a normal distribution. To achieve this goal, we applied several methods, such as checking the frequency distribution, calculating the skewness and kurtosis values, and using the Shapiro-Wilk test. Because of the small size of LEP data and the non-normal distribution of several groups, we adopted non-parametric statistical methods. Friedman’s test was performed first to compare the latency and amplitude of each LEP component on the control side and painful side at three different time points (day 1, day 4, and day 7). Once the result showed a significant difference, the Wilcoxon signed-rank test was performed for the pairwise comparison. Data were presented as median values.

Since we were interested in the characteristic changes of the N2-P2 wave complex at three different time points (day 1, day 4, and day 7) under DRGS treatment, we compared the three values of N2-P2 amplitude. Meanwhile, for each component (N2 and P2), the latency and amplitude of each side (painful side and control side) were compared, respectively.

Regarding the long-lasting effect of DRGS therapy, we also employed Wilcoxon signed-rank test to compare the N2-P2 amplitude of the painful side in the ON and OFF status of the DRGS system. Besides, NRS at four different time points (pre, day 1, day 4, and day 7) under DRGS treatment were also compared by using the Friedman test and Wilcoxon signed-rank test.

For the oscillatory activity of gamma band, the gamma band was divided into lower frequency gamma band (30-45 Hz) and higher frequency gamma band (55-95 Hz). After testing for normal distribution, for each frequency band, the gamma band power of two different time points (day 1 and day 7) were compared by paired student *t* tests. For the correlation of gamma band power and NRS, Spearman correlation tests were performed on the lower frequency gamma band and the higher frequency gamma band, respectively with NRS.

3. Results

3.1 LEP results

3.1.1 N2 component

For the latency of the N2 component, a Friedman test was carried out to compare the latencies at three different time points (day 1, day 4, and day 7). On the control side, the results showed there was no significant difference among the time points ($\chi 2(2) = 1.697$, $p = 0.428$). The median values of the N2 latencies at three time points were 200.00 ms, 204.00 ms, and 188.00 ms, respectively. However, on the painful side, the results showed that there was no significant difference among the time points ($\chi 2(2) = 1.200$, $p = 0.549$). The median values of N2 latencies at three time points were 204.00 ms, 212.00 ms, and 208.00 ms, respectively (Figure 3.1).

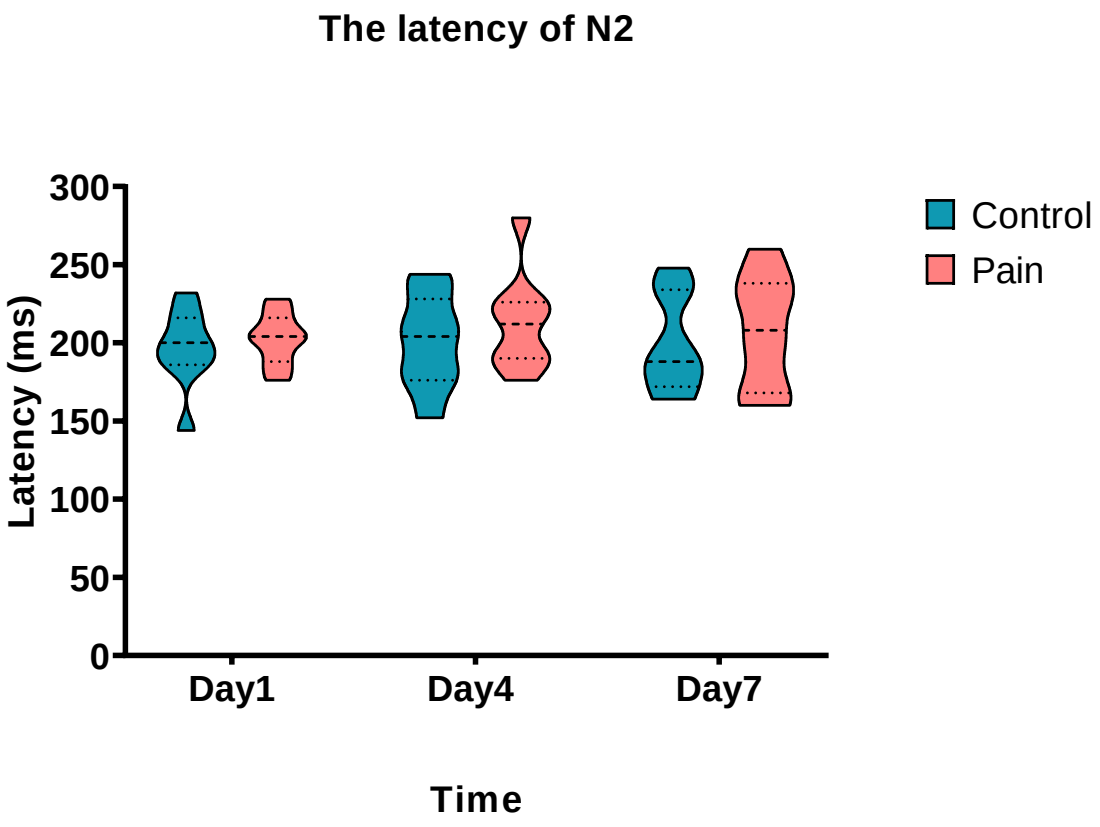

Figure 3. 1 A violin plot of N2 latency

The violin plot shows the N2 latency on the control side and the painful side at three different time points (day1, day4, and day7). There was no significant difference in latency on the control side or the painful side.

For the amplitude of the N2 component, we used the Friedman test to compare the amplitudes at three different time points (day 1, day 4, and day 7). On the control side, the results showed there was no significant difference among the time points ($\chi2(2) = 0.000$, $p = 1.000$). The median values of the N2 amplitudes at three time points were -3.11 μV, -3.28 μV, and -3.09 μV, respectively. However, on the painful side, the results showed there was a significant difference among the time points ($\chi2(2) = 6.889$, $p = 0.032$). The median values of the N2 amplitudes at three time points were -1.39 μV, -1.67 μV, and -2.88 μV, respectively. The Wilcoxon signed-rank test showed there was no significant difference among day1 and day 4 ($Z = -1.007$, $p = 0.314$), day 4 and day 7

(Z = -1.244, p = 0.214), respectively. However, there was a significant difference between day 1 and day 7 (Z = -2.666, p = 0.008) (Figure 3.2).

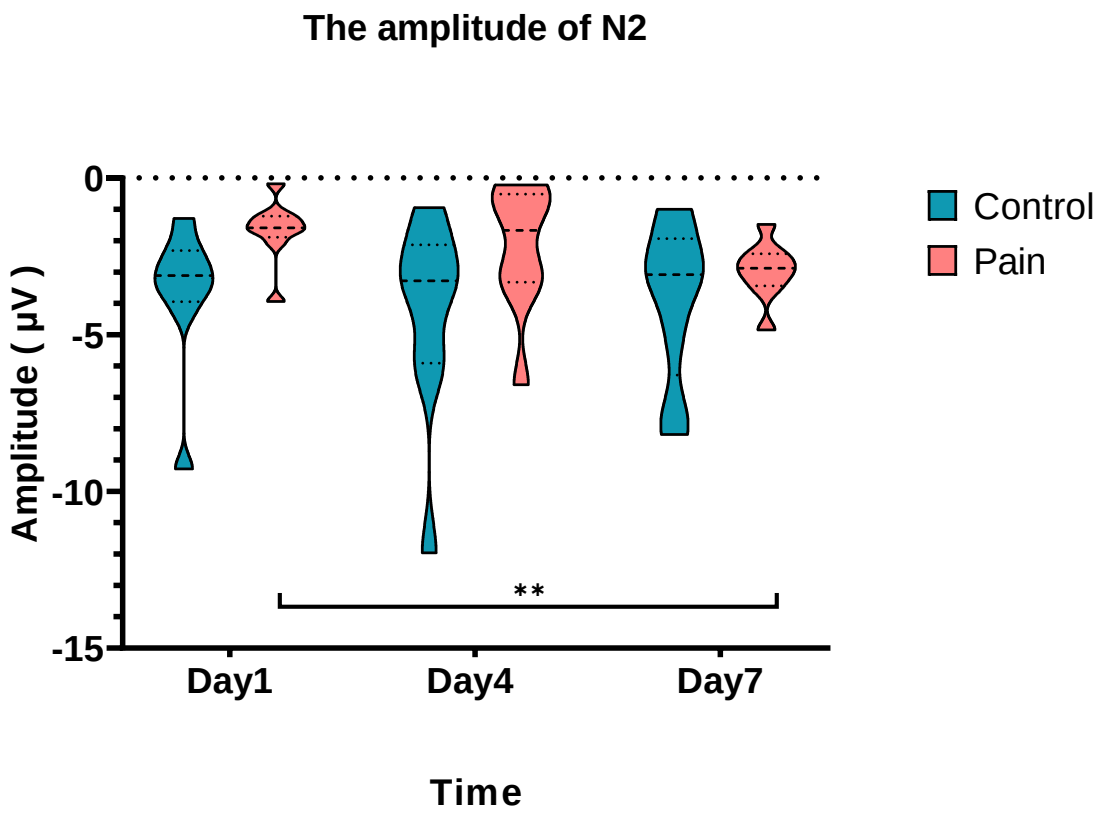

Figure 3. 2 A violin plot of N2 amplitude

The violin plot shows the N2 amplitude on the control side and the painful side at three different time points (day 1, day 4, and day 7). On the painful side, there was a significant increase in the amplitude from day 1 to day 7 (p = 0.008). ** indicates p < 0.01.

3.1.2 P2 component

For the latency of the P2 component, we also employed the Friedman test to compare the latencies at three different time points (day 1, day 4, and day 7). On the control side, the results showed there was no significant difference among the time points ($\chi 2(2)$ = 0.222, p = 0.895). The median values of P2 latencies at three time points were 384.00

ms, 384.00 ms, and 380.00 ms, respectively. However, on the painful side, the results showed there was no significant difference among the time points ($\chi 2(2) = 0.941$, $p = 0.625$). The median values of the P2 latencies at the three time points were 384.00 ms, 380.00 ms, and 368.00 ms, respectively (Figure 3.3).

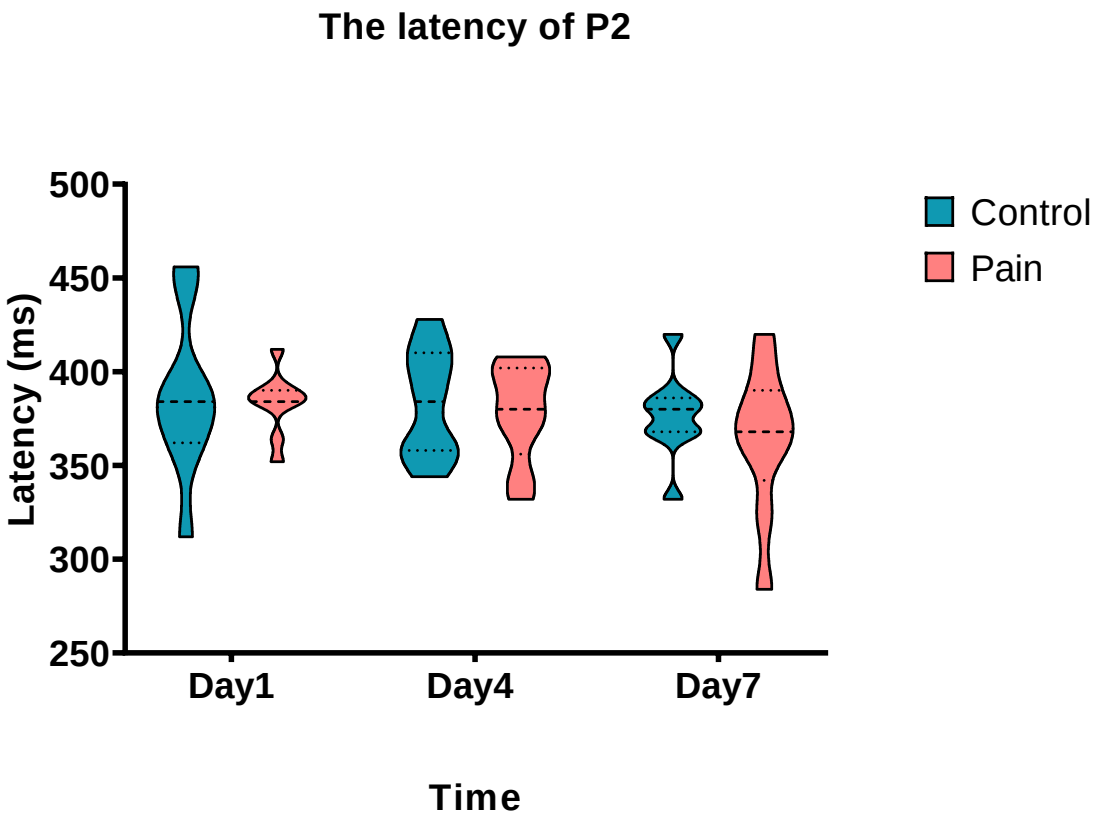

Figure 3. 3 A violin plot of P2 latency

The violin plot shows the P2 latency on the control side and the painful side at three different time points (day 1, day 4, and day 7). There was no significant difference in latency on the control side or the painful side.

For the amplitude of the P2 component, we used the Friedman test to compare the amplitudes at three different time points (day 1, day 4, and day 7). On the control side, the results showed there was no significant difference among the time points ($\chi 2(2) = 1.556$, $p = 0.459$). The median values of P2 amplitudes at three time points were 4.65

μV, 3.64 μV, and 4.49 μV, respectively. However, on the painful side, the results showed there was significant difference among the time points ($\chi 2(2) = 12.667$, $p = 0.002$). The median values of P2 amplitudes at three time points were 1.61 μV, 3.09 μV, and 4.53 μV, respectively. The Wilcoxon signed-rank test showed there was no significant difference among day 4 and day 7 ($Z = -1.718$, $p = 0.086$). There was a significant difference between day 1 and day 4 ($Z = -2.547$, $p = 0.011$), day 1 and day 7 ($Z = -2.666$, $p = 0.008$), respectively (Figure 3.4).

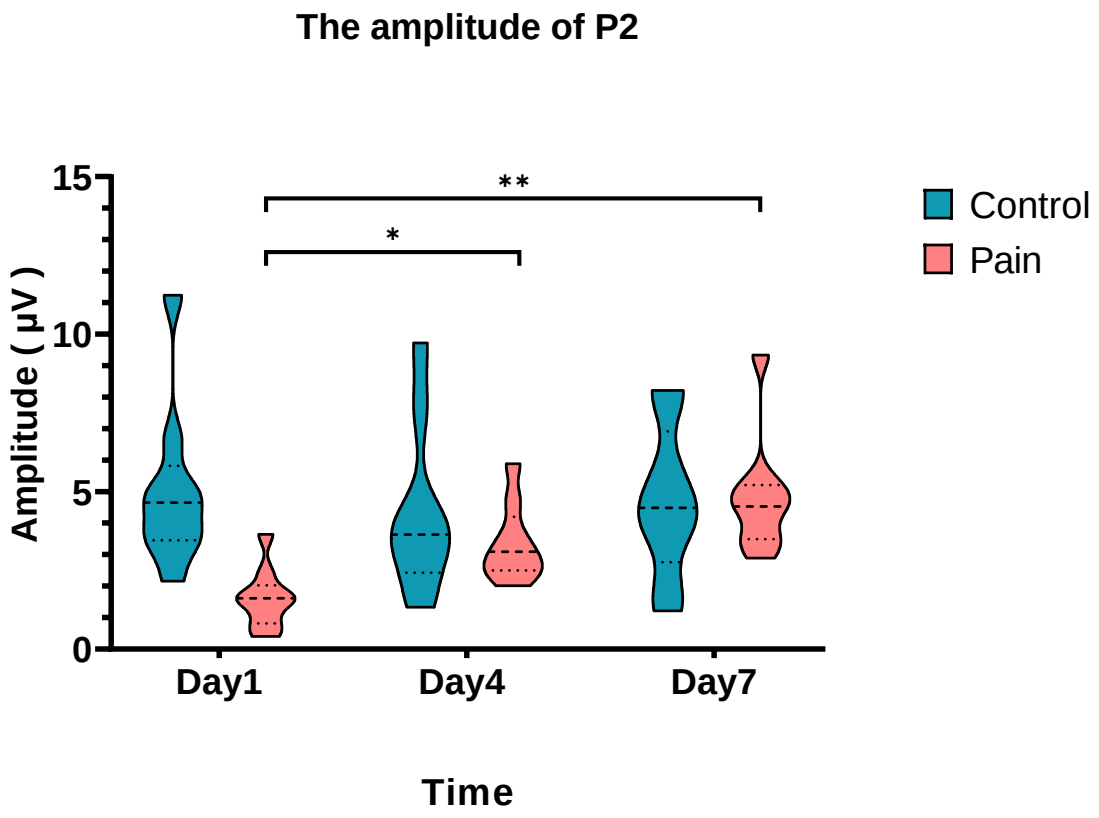

Figure 3. 4 A violin plot of P2 amplitude

The violin plot shows N2 amplitude on the control side and the painful side at three different time points (day 1, day 4, and day 7). On the painful side, there was a significant increase in amplitude from day 1 to day 4 ($p = 0.011$), day 1 to day 7 ($p = 0.008$). * indicates $p < 0.05$, ** indicates $p < 0.01$.

3.1.3 N2-P2 complex

For the N2-P2 complex, a Friedman test was carried out to compare the effects of amplitudes of the N2-P2 complex at three different time points (day 1, day 4, and day 7). On the control side, the results showed there was no significant difference among the time points ($\chi2(2) = 0.889$, $p = 0.641$). The median values of N2-P2 amplitudes at three time points were 8.02 μV, 6.92 μV, and 9.39 μV, respectively. However, on the painful side, the result showed there was a significant difference among the time points ($\chi2(2) = 14.222$, $p = 0.001$). The median value of N2-P2 amplitudes at three time points were 3.27 μV, 5.67 μV, and 7.60 μV, respectively. The Wilcoxon signed-rank test showed there was a significant difference between day 1 and day 4 ($Z = -2.429$, $p = 0.015$), day 4 and day 7 ($Z = -2.547$, $p = 0.011$), day 1 and day 7 ($Z = -2.666$, $p = 0.008$), respectively (Figure 3.5). The grand average of N2-P2 complex shows the evolution of LEP from day 1 to day 4 and day 7 (Figure 3.6).

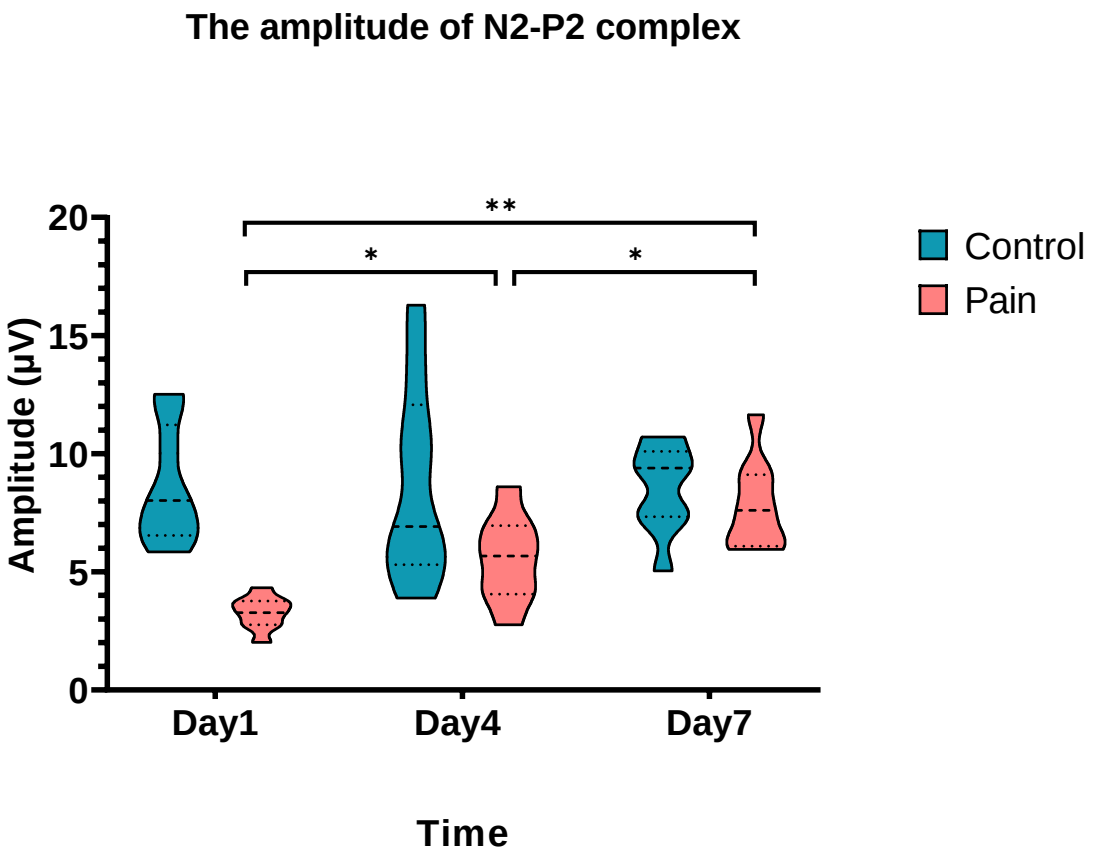

Figure 3. 5 A violin plot of N2-P2 complex's amplitude

The violin plot shows N2-P2 complex's amplitude on the control side and the painful side at three different time points (day 1, day 4, and day 7). On the painful side, there was a significant increase in amplitude from day 1 to day 4 ($p = 0.015$), day 4 to day 7 ($p = 0.011$), and day 1 to day 7 ($p = 0.008$). * indicates $p < 0.05$, ** indicates $p < 0.01$.

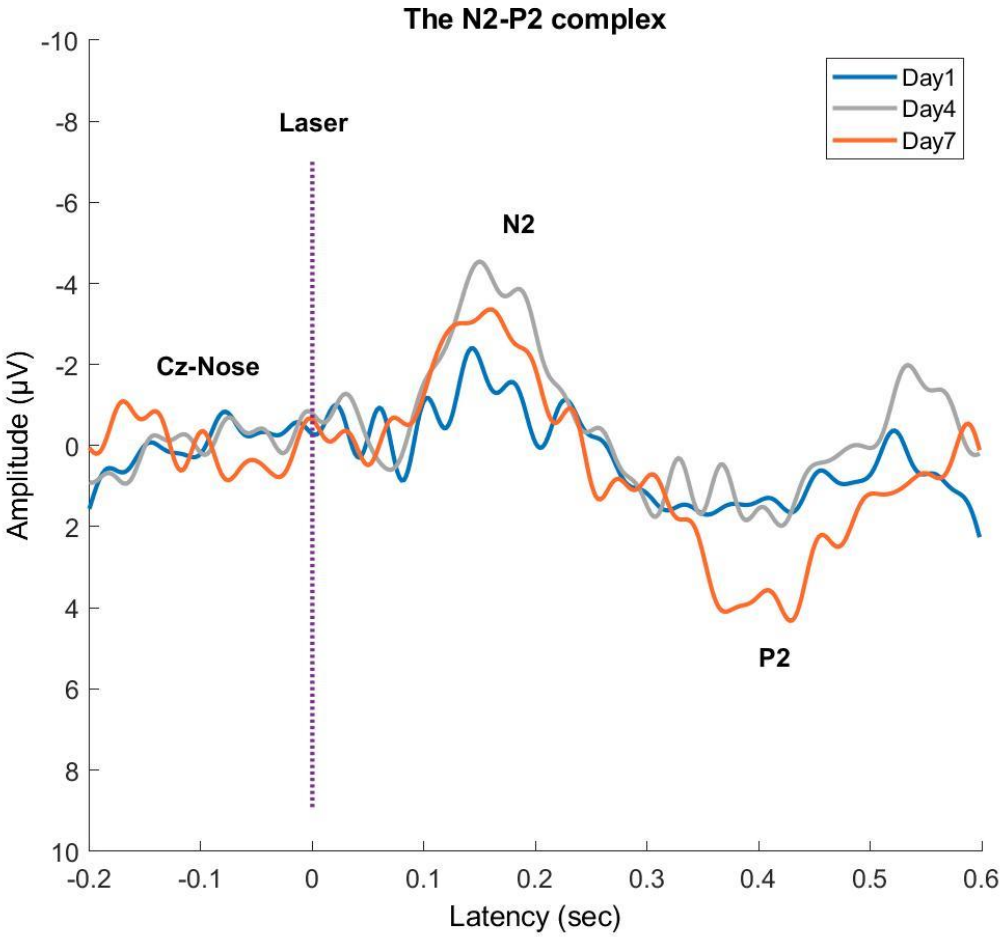

Figure 3. 6 The grand average of N2-P2 complex

This figure shows the evolution of LEP from day 1 to day 4 and day 7. There was no LEP on day 1, and the LEP was restored on day 7.

3.1.4 Comparison of N2-P2 complexes in DRGS ON and OFF states

The amplitudes of the N2-P2 complex at three different time points (day 1, day 4, and day 7) under two conditions (DRGS ON and OFF) on the painful side were compared by Wilcoxon signed-rank test, respectively. In the state of DRGS ON, the median values of N2-P2 amplitudes at three time points were 3.27 μV, 5.67 μV, and 7.60 μV, respectively. In the state of DRGS OFF, the median values of N2-P2 amplitudes at three time points were 2.92 μV, 5.83 μV, and 7.27 μV, respectively. The Wilcoxon

signed-rank test showed that there was no significant difference between the two conditions (DRGS ON and OFF) on day 1 (Z = -0.770, p = 0.441), day 4 (Z = -0.652, p = 0.515), and day 7 (Z = -0.296, p = 0.767), respectively (Figure 3.7).

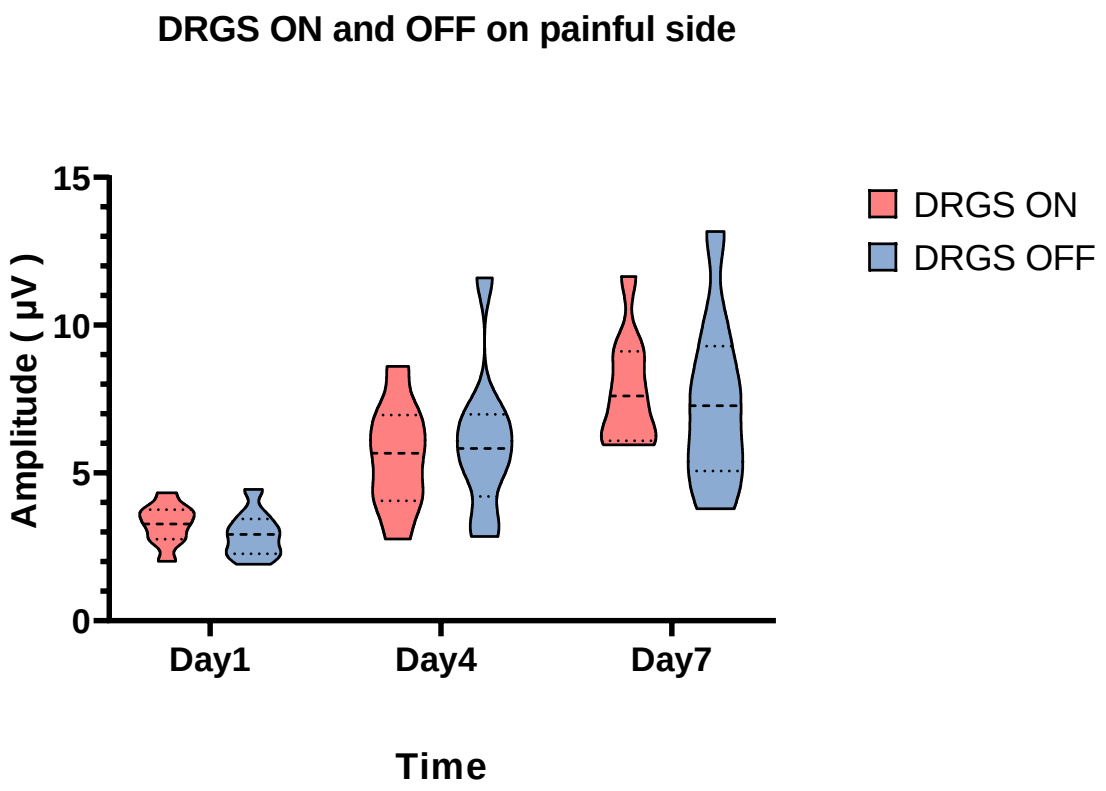

Figure 3. 7 A violin plot of N2-P2 complex amplitudes in DRGS ON and OFF states
The violin plot shows N2-P2 complex amplitudes of the painful side in DRGS ON and OFF states at three different time points (day 1, day 4, and day 7). There was no significant difference between DRGS ON and OFF states.

3.2 NRS results

As with the NRS results at four different time points (pre, day 1, day 4, and day 7), we also performed a Friedman test to compare the four values. The results showed there was significant difference among the time points ($\chi 2(2)$ = 20.316, p < 0.001). The median values of NRS at four time points were 7.00, 2.00, 2.00, and 2.00, respectively. The Wilcoxon signed-rank test showed there was significant difference between pre and

day 1 (Z = -2.716, p = 0.007), pre and day 4 (Z = -2.669, p = 0.007), pre and day 7 (Z = -2.669, p = 0.007), day 1 and day 4 (Z = -2.000, p = 0.046), respectively. There was no significant difference among day 1 and day 7 (Z = -1.667, p = 0.096), day 4 and day 7 (Z = -0.378, p = 0.705), respectively (Figure 3.8).

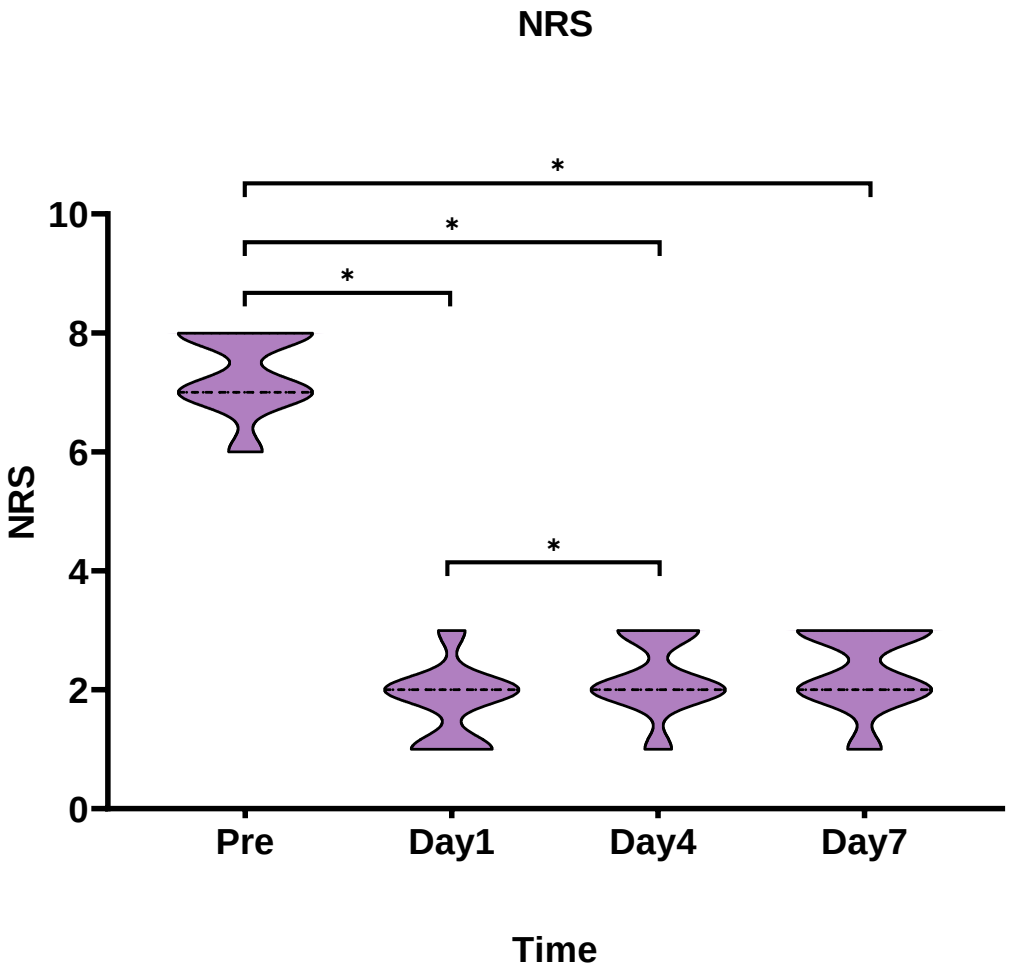

Figure 3. 8 A violin graph reveals the NRS in all subjects

Compared with the preoperative measurement, patients' NRS significantly decreased after 1 day (p = 0.007), 4 days (p = 0.007), and 7 days (p = 0.007). From day 1 to day 4, the NRS increased significantly (p = 0.046). * indicates $p < 0.05$.

3.3 Gamma band power results

For the lower gamma band (30-45 Hz) power, we performed a paired student *t* test to show the difference between day 1 and day 7. On day 1 and day 7, the average powers were 0.61±0.42 uV^2/Hz and 0.25±0.10 uV^2/Hz, respectively. The decreased value was 0.37± 0.36 uV^2/Hz, and 95% of confidence interval was from 0.09 to 0.64 uV^2/Hz. The result showed there was a significant decrease in lower gamma band (30-45 Hz) power from day 1 to day 7 ($t = 3.076$, $p = 0.015$) (Figure 3.9).

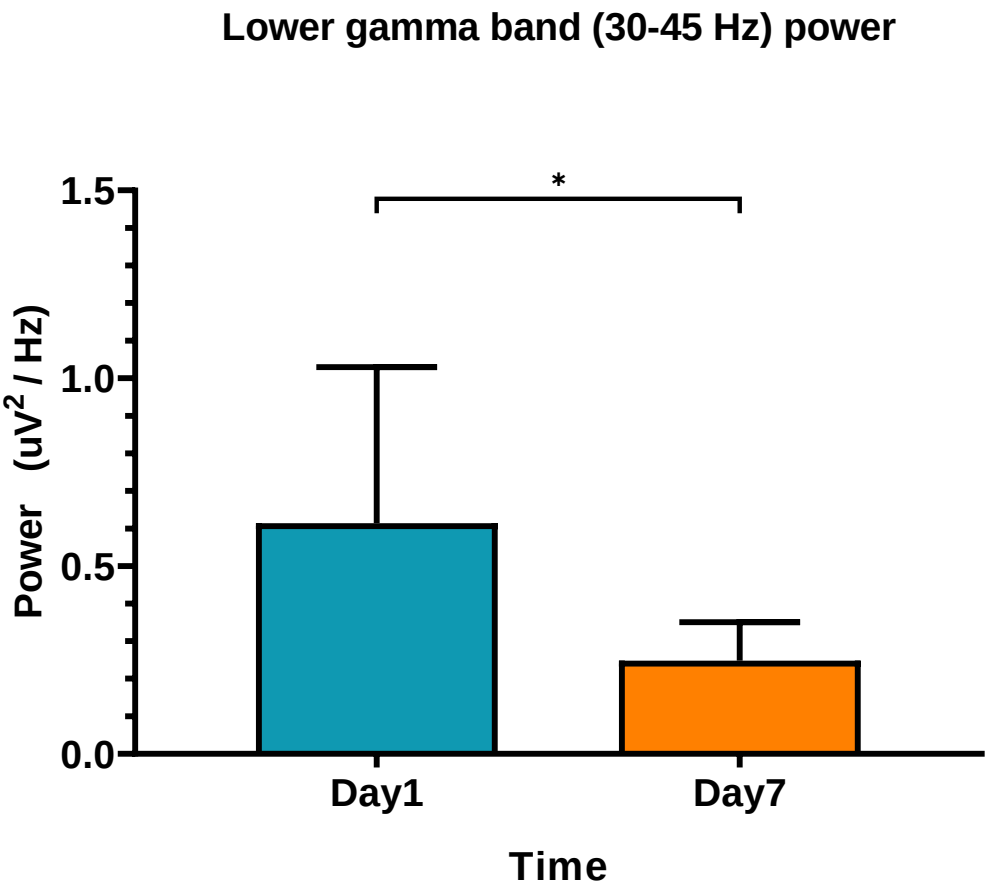

Figure 3. 9 A bar graph of the lower gamma band (30-45 Hz) power in all subjects
The bar graph shows lower gamma band power on day 1 and day 7. There was a significant decrease in lower gamma band (30-45 Hz) power from day 1 to day 7 ($t = 3.076$, $p = 0.015$). * indicates $p < 0.05$.

Yet for the higher gamma band (55-95 Hz) power, we also performed a paired student *t* test to show the possible difference between day 1 and day 7. On day 1 and day 7, the average powers were 0.36±0.26 uV^2/Hz and 0.18±0.08 uV^2/Hz, respectively. The decreased value was 0.18± 0.25 uV^2/Hz, 95% confidence interval was -0.01 to 0.37 uV^2/Hz. The result showed that there was a decrease in higher gamma band (55-95 Hz) power from day 1 to day 7 ($t = 2.146$, $p = 0.064$) (Figure 3.10).

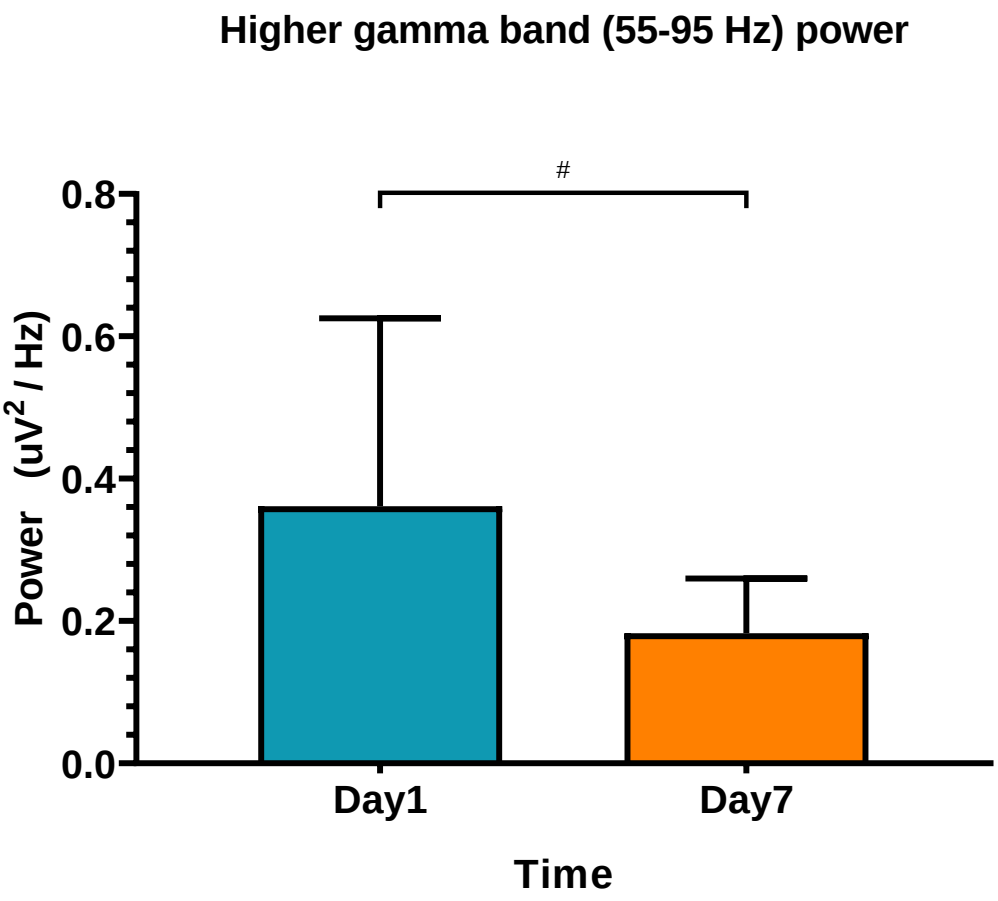

Figure 3. 10 A bar graph of the higher gamma band (55-95 Hz) power in all subjects The bar graph shows higher gamma band power on day 1 and day 7. There was a decrease in the higher gamma band (55-95 Hz) power from day 1 to day 7 ($t = 2.146$, $p = 0.064$). # indicates $p < 0.1$

3.4 Spearman correlation between gamma band power and NRS

We employed the Spearman correlation to analyze the relationship between lower gamma band (30-45 Hz) power and NRS on day 1 and day 7. The result showed that the lower gamma band power was positively correlated with the NRS (Spearman $r = 0.4946$, $p = 0.037$) (Figure 3.11).

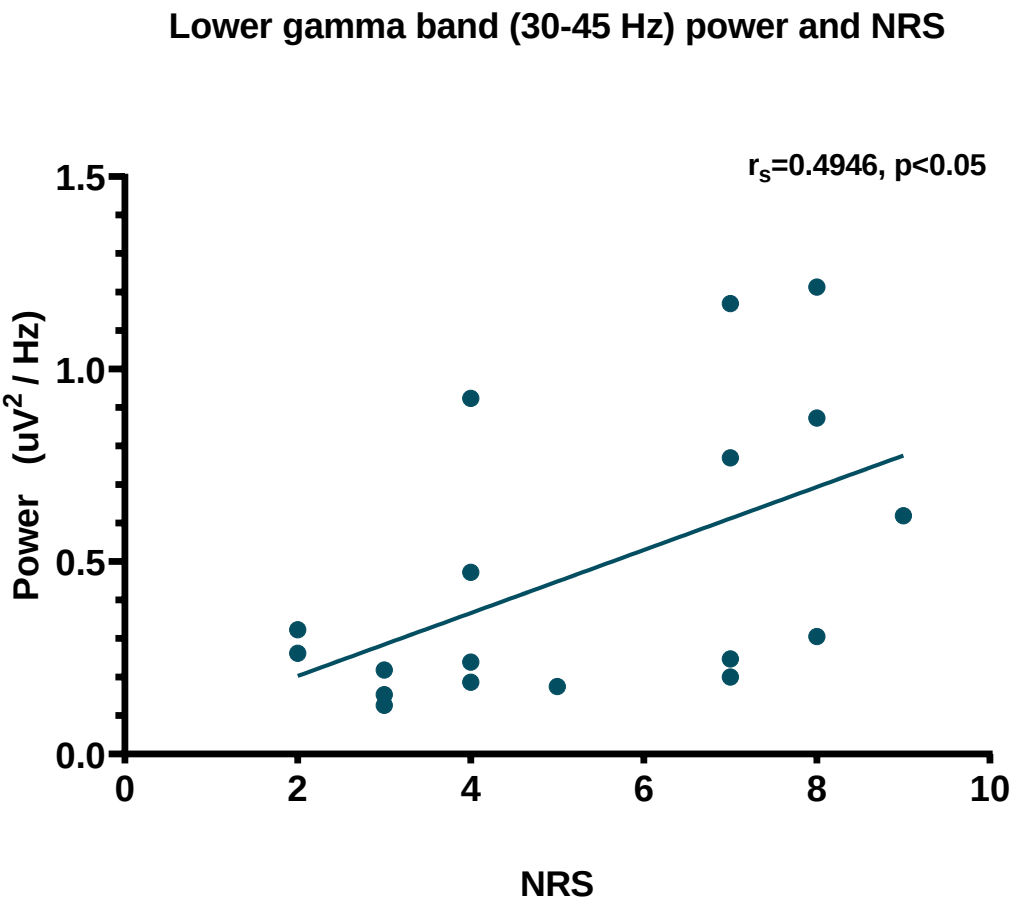

Figure 3. 11 Lower gamma band (30-45 Hz) power and NRS

The plot shows that there was a positive correlation between lower gamma band (30-45 Hz) power and NRS on day 1 and day 7 (Spearman $r = 0.4946$, $p = 0.037$).

Meanwhile, we also employed the Spearman correlation to analyze the relationship between the higher gamma band (55-95 Hz) power and NRS on day 1 and day 7. The

result showed that higher gamma band (55-95 Hz) power was positively correlated with NRS (Spearman $r = 0.464$, $p = 0.052$) (Figure 3.12).

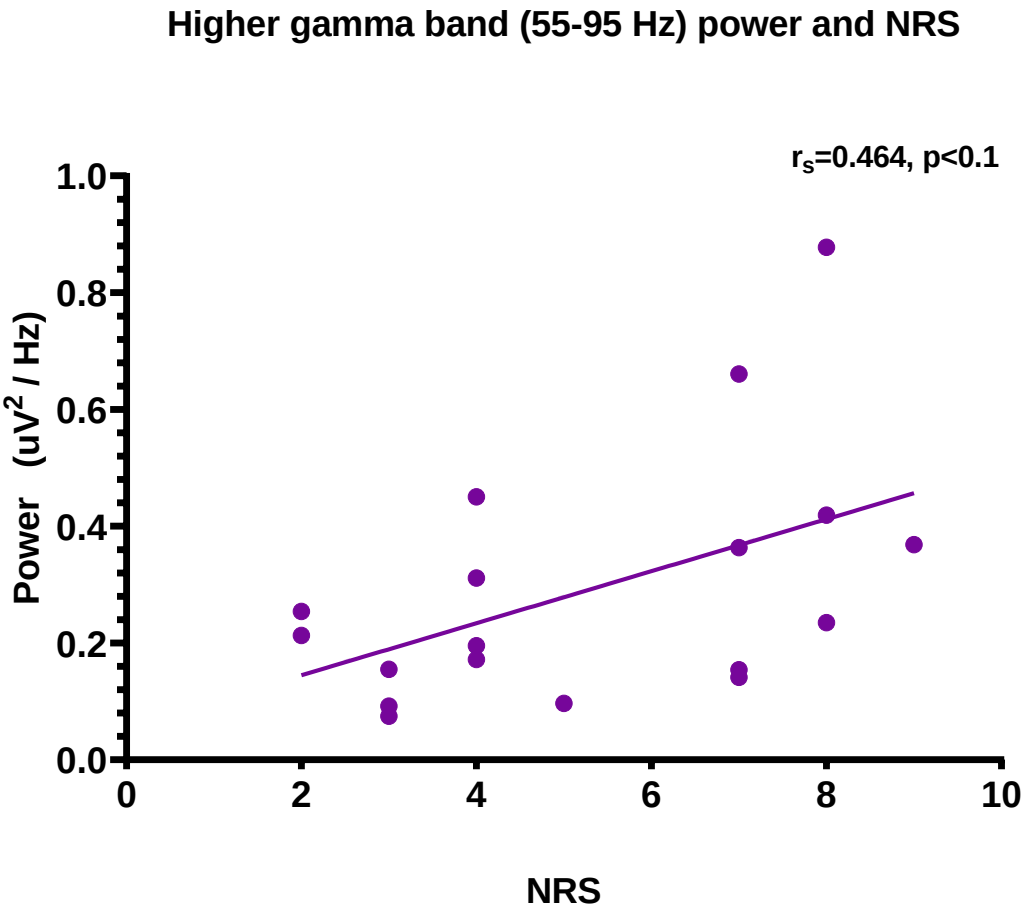

Figure 3. 12 Higher gamma band (55-95 Hz) power and NRS

The plot shows there was a positive correlation between higher gamma band (55-95 Hz) power and NRS on day 1 and day 7 (Spearman $r = 0.464$, $p = 0.052$).

4. Discussion

4.1 The neurophysiological mechanisms of pain processing pathways

So far, our knowledge of the mechanisms of neuropathic pain has still been incomplete. Although a lot of experiments have revealed several related mechanisms, we still lack a complete understanding of it. In the past decades, most of our experience has come from basic medical research, but it still has some practical significance when applied to the clinic (Costigan, Scholz, & Woolf, 2009). Besides, neuropathic pain always involves many different mechanisms (Baron, Binder, & Wasner, 2010), which undoubtedly increase the breadth and difficulty of the research.

As was reported, the damage of afferent pathways is one of the important and necessary features in the development of neuropathic pain (Baron, 2006). The activation of nociceptors is the first step of pain propagation. Nociceptors are the distal parts of the primary afferent neurons that are widely distributed in most tissues such as skin, muscles, joints, viscera and blood vessels, and can be activated by mechanical, thermal, and chemical stimuli. In the human peripheral nervous system, there are mainly three sensory fibers: A-β fibers, A-δ fibers, and C fibers. This classification is based on its own structure and physiological function. Under normal physiological conditions, A-β fibers are myelinated and approximately 10 μm in diameter. The conduction speed is about 30-100 m/s, which is the fastest among these three types of fibers. It can quickly transmit action potentials from the periphery to the central areas. A-δ fibers are also myelinated and are about 2.0-6.0 μm in diameter, the conduction speed is about 12-30 m/s. C fibers are unmyelinated and are about 0.4-1.2 μm in diameter. The conduction speed is about 0.5-2.0 m/s (Almeida, Roizenblatt, & Tufik, 2004). In general, different structures determine different functions. These fibers conduct various signals from the

periphery to the spinal dorsal horn. A-δ fibers and C fibers have higher activation thresholds than A-β fibers, which can be selectively activated by painful or harmful stimuli. Therefore, A-δ fibers and C fibers are also called pain fibers (D'mello & Dickenson, 2008).

A-δ fibers have two different subtypes in category, each of which performs several different functions. The type I group mainly consists of high threshold mechanoreceptors, which primarily respond to high intensity mechanical stimuli and to thermal or chemical stimuli. The Type II group mainly contains high temperature (45-53 ° C) mechano-thermal receptors and low temperature (-15 ° C) receptors, which primarily respond to mechanical, thermal and cold stimuli (Millan, 1999). C fibers primarily contain mechanoreceptors, temperature-sensitive receptors, chemical receptors and several special receptors (Wu et al., 2002). They can respond to multiple types of stimulation, and, therefore, they are also called polymodal.

From an anatomical and neurophysiological perspective, nociceptive signals can be transmitted to the spinal cord from the periphery to the central parts via primary afferent fibers (A-β, A-δ, and C fibers). In the past, the DRG was considered as a passive structure, which supposedly was conveying information only. As the research progressed, the results showed that it was also an active participant in pain transmission, which became the basis for neuromodulation therapies (Krames, 2015). Most A-δ and C fibers terminate in laminae I and II of the spinal dorsal horn. Laminae I contain most projection neurons which can propagate the nociceptive information to the upper central areas. The signal is delivered to special brain areas such as thalamus, the periaqueductal grey, and the prefrontal area (Todd, 2002). In addition, the thalamus also receives a large amount of sensory information from projection neurons of the laminae III-VI, and most of the sensory components of the pain experience come from this ascending pathway (D'mello & Dickenson, 2008). Subsequently, the signal is projected onto the

cerebral cortex from the thalamus. During this process, a number of other active brain regions such as primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices together with thalamus constitute the so-called pain matrix (Tracey & Mantyh, 2007) (Figure 4.1).

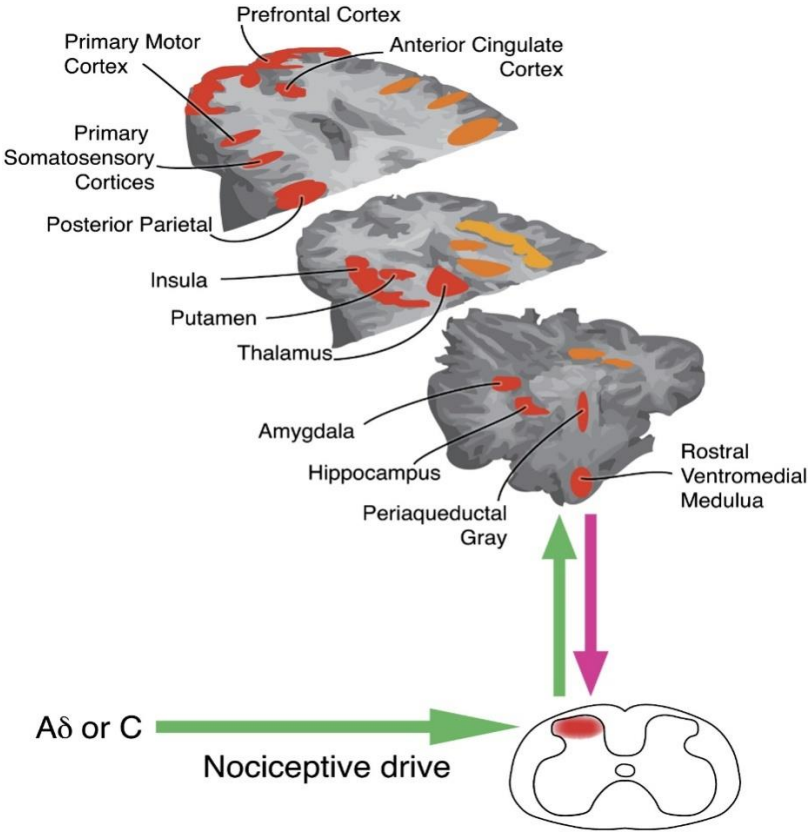

Figure 4. 1 Sketch of pain processing pathway (Tracey & Mantyh, 2007)

Nociceptive stimuli activate A-δ and C receptors which generate impulse information transmitted to the dorsal horn of the spinal cord through the DRG. Projection neurons transmit the nociception to areas such as the thalamus through ascending pathways, and then are projected onto the cerebral cortex.

4.2 Restored LEP and decreased NRS in neuropathic pain patients under DRGS treatment

The pain pathway constitutes one part of somatosensory system (Rolf-Detlef Treede, 2003). For a long time, somatosensory evoked potentials (SEP) were considered as an

effective tool for the assessment of the somatosensory pathways. This tactile and proprioceptive system can reflect the functions of large fibers, the dorsal columns of the spinal cord. In other words, it is difficult to use this method to detect the functions of other somatosensory systems such as temperature and pain sensation pathways. With the application of the CO_2 laser (Mor & Carmon, 1975), it is accessible to explore the pain pathways of the somatosensory systems. The A-δ and C nociceptors can be selectively activated by the laser radiant heat pulses (Bromm & Treede, 1983). Among a wide variety of laser systems, the CO_2 laser is the most commonly used in pain research field. The wavelength of it is 10.6 μm and the energy loss caused by skin reflex is almost negligible(Arendt-Nielsen & Chen, 2003). Besides, the laser pulses can be absorbed by the skin and the thermal effects cause only nociceptors to be stimulated and not others such as mechanoreceptors (Bromm & Lorenz, 1998). For this reason, most of the studies employ the CO_2 laser system.

Just like other human physiological data, it is also important to obtain normative values for LEP data. Some factors such as stimulus intensity, body region and body height may also influence the LEP. Some researchers have observed that as the intensity of the stimulus increases, the amplitude of the trigeminal LEP will also increase (Romaniello, Arendt-Nielsen, Cruccu, & Svensson, 2002; R-D Treede, Kief, Hölzer, & Bromm, 1988). However, in our study, in order to protect the patient's skin from burns or overheating and to obtain LEP at the same time, the intensity of the laser stimulation was determined by the patient's pain threshold. We set the NRS pain threshold at about four. Different body regions have different numbers of nociceptors that can transmit acupuncture pain. It has already been proven that the A-δ nociceptors are denser at the proximal end than at the distal body parts by skin biopsy experiments (Lauria et al., 1999). R. Agostino et al. have also demonstrated that there is a positive correlation between pinprick threshold and the distance from the brain (Agostino et al., 2000). These results indicate that a higher amplitude response may be obtained when a

pinprick stimulation is performed on a body part closer to the brain. In addition, the variance of body height may also influence the LEP. Truini et al. recruited 100 healthy volunteers and measured their thresholds, latencies, and amplitudes of the main components (N2 and P2) on different parts of the body (perioral, hand, and foot) (Truini et al., 2005). They have shown that the latency of the LEP is related to height, while the amplitude of the LEP is related to age. There is no significant difference between genders. However, the age of volunteers was negatively correlated with the amplitude of LEP. With the increase of age, there may be neuronal loss or dysfunction in the central and peripheral nervous systems (Gagliese & Melzack, 2000). This is the reason why our patients' amplitude of the LEP is not as large as in young healthy volunteers. In order to define the characteristics of the LEP components, many studies have been undertaken in last thirty years (Bromm & Treede, 1987; Kakigi et al., 1989; Kunde & Treede, 1993). In earlier studies, it has been shown that A-δ and C fibers could be activated by transient CO_2 laser radiation heat pulses. Researchers have also found out that the accompanying late and ultra-late evoked potentials could be used for the identification of first and second pain. In our research, the target LEP is the late component. Its maximum amplitude appears at the vertex (Bromm & Lorenz, 1998), which also indicates the integrity of the A-δ pain pathway. The negative and positive components constitute a peak-to-peak complex, and its amplitude is the focus of research. In many pain-related clinical studies, the characteristics of the LEP components have been described in detail (Quante, Lorenz, & Hauck, 2010; Truini et al., 2010; Uglem, Omland, Stjern, Gravdahl, & Sand, 2017). In our group's previous study, a number of localized neuropathic pain patients were recruited and their LEPs were measured. The results showed that the N2-P2 amplitude increased significantly at one month and six month when compared to the baseline (Morgalla et al., 2019). In addition, patients' quality of life was significantly improved at six months when compared to the baseline. This finding has demonstrated that LEP can recover after six months under DRGS treatment. But in the present study, we have also proven that the LEP amplitude can recover within seven days. Compared

to day 1, the N2-P2 amplitude increased significantly on day 4 and on day 7. However, when compared to the previous study, the amplitude of the LEP is not as large as before, because the LEP may still need some more time in order to recover under DRGS treatment.

In this study, we investigated the characteristics of the N2 and P2 components separately. The latency of the N2 component was not significantly different between the control side and the painful side, but the amplitude of the N2 component showed a significant increase on day 7 when compared to day 1. Similar findings were found in the P2 component. The latency of the P2 component was not significantly different between the control side and the painful side, but the amplitude increased significantly on day 4 and day 7 when compared to day 1. The increase in amplitude may be related to the characteristics of the component itself or the information transmission process in the nervous system. The N2-P2 complex can be regarded as a sign of A-δ fiber activation, which means that this pain conduction pathway is unblocked. As far as we know, it is likely that N2 originates from the insular cortex and anterior cingulate cortex, while P2 originates from the anterior cingulate cortex (Garcia-Larrea et al., 2003). Treede et al. found that in the patients with syringomyelia, the P2 component was affected (R-D Treede et al., 1991). In one study of healthy volunteers, researchers have shown that placebo effect and reduced intensity of laser stimulation can reduce the P2 amplitude, not the N2 amplitude (Wager, Matre, & Casey, 2006). In another healthy volunteer study, the author also showed that antinociceptive drugs can reduce the amplitude of the N2 and P2 components (Truini et al., 2010). In our study, we found that the patients' N2-P2 amplitude recovered after DRGS treatment, and the increased amplitude of N2 and P2, which can be considered as the recovery of A-δ pain processing. We also found that after the DRGS system has been turned OFF, the amplitude of the LEP has not changed significantly when compared to the DRGS system which has been turned ON. The results suggest that DRGS may have a lasting rather than a transient effect.

In addition, changes in NRS can also show the very good analgesic effect of DRGS. From pre-surgery to one day after DRGS surgery, the patient's NRS decreased significantly. During the next two time points of the evaluation (day 4 and day 7), NRS also indicated a significant decrease when compared to pre-surgery. This trend in NRS is consistent with previous long-term follow-up publications on DRGS (Morgalla et al., 2017). Interestingly, there was a slight increase in NRS from day 1 to day 4. We know that patients are always taking additional pain medication after the operation in order to relieve post-operative pain.

4.3 Decreased gamma band activity in neuropathic pain patients under DRGS treatment

The activity of nerve cell populations plays an important role in maintaining brain functions. These cells have common characteristics of oscillation and synchronization over a wide frequency range which are strongly associated with behavioral states (Salinas & Sejnowski, 2001). This activity can be strongly correlated with the flow of information in the brain, which represents a response to related events or behavioral states. Brain neural oscillation represents the sensory information selection, integration, and propagation in the nervous system (Ploner, Sorg, & Gross, 2017). To some extent, the oscillations of the brain represent the excitability of the sensory and motor systems in the central nervous system (Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006). As mentioned earlier, the areas of the brain associated with the pain matrix involve different steps of sensory information transmission and are presented at frequencies from 3 to 100 Hz (Gross et al., 2007). In oscillatory activities of different frequency bands, the activity of the gamma band has proven to play a key role in the process of acute pain and chronic pain (Schulz et al., 2015).

The gamma band was considered as an active participant in pain processing in the somatosensory system. In healthy adults, researchers have shown that high frequency

(60-95 Hz) gamma oscillations at the somatosensory cortex can be activated by painful stimuli (Gross et al., 2007). In this study, the author employed magnetoencephalography (MEG) to record the responses of contralateral primary (S1) and bilateral secondary (S2) somatosensory cortices by the way of painful laser stimuli. The result indicates that gamma oscillations in S1 are relevant to the subjective pain perception. Besides, researchers have also done some exploratory work in patients with chronic neuropathic pain. In clinical practice, chronic neuropathic pain is one of the intractable diseases, which is difficult to treat and long lasting. The disease involves many unknown mechanisms, which makes it also to be an attractive field of research. Lim et al. have shown an enhanced gamma band power in fibromyalgia patients (Lim et al., 2016). Fibromyalgia is considered as a disease that can alter the function or structure of the thalamus. In this study, MEG was applied to record the spontaneous brain activity. The results showed that oscillating activities with both low and high frequencies in patients increased when compared to healthy volunteers. Meanwhile, the corresponding brain regions were related to the pain regulation and cognition. In another study, Rui et al. proved significantly increased gamma band power in post-herpetic neuralgia (PHN) patients (Zhou et al., 2018). PHN is a common disease in the clinical practice, which has a typical feature of neuropathic pain. Based on power spectrum analysis, the author found that the gamma band (40-70 Hz) power of patients with PHN was significantly higher than that of healthy volunteers. Besides, the gamma band oscillatory activity was also positively correlated with the pain intensity. When compared to these studies, our study employed longitudinal comparisons at different time points. We wanted to examine possible electrophysiological changes in neuropathic pain patients undergoing DRGS treatment. The results showed that both lower gamma band power and higher gamma band power were significantly reduced, which also indicates that the gamma band power may be a suitable biomarker for evaluating the therapeutic effect of patients with neuropathic pain. Most of the previous studies were focused on the enhanced gamma band activities in various pain conditions. We examined changes in gamma band

power in neuropathic pain patients and found a decreased power in gamma band after DRGS treatment for the first time. Our study specifically targeted the gamma band activity of chronic neuropathic pain patients with DRGS treatment, and the results showed that the lower (30-45 Hz) and higher (55-95 Hz) gamma band power were both reduced on day 7 when compared to day 1. These findings provide evidence towards possible reduction in excitability of brain neurons in neuropathic pain patients after one week's DRGS treatment. The results also showed the advantage of DRGS therapy in neuropathic pain patients from the neurophysiological perspective.

In addition, our results show that the power of the gamma band is positively correlated with the pain intensity. In our study, the patients always reported about pain relief after the DRGS treatment. Therefore, we used the NRS to assess the pain conditions of patients on day 1, day 4 and day 7 after implantation of the DRGS system. The Spearman correlation analysis has shown that both lower and higher gamma band powers are positively correlated with NRS. Our findings are consistent with those of previous experimental results. In an animal experiment, the authors recorded the spontaneous ECoG of rats with chronic inflammatory pain. The power spectrum analysis of the ECoG demonstrated that the gamma band power was enhanced in rats which suffered from chronic pain. At the same time, the gamma band power was also positively correlated with the pain intensity of rats (Wang et al., 2016). In another clinical study, the authors also reported that gamma activity was strongly correlated with the pain intensity. Interestingly, they reported one special case of reduced gamma power after pain relief (Zhou et al., 2018). Our findings are consistent with their report. That means, the more severe the pain is, the higher both the corresponding NRS, and the gamma band power will be. On the other hand, the lower the pain is, the lower both the corresponding NRS, and the gamma band power will be. But the difference is that our experiment dynamically follows on and measures the changes in the patient's gamma band power under DRGS treatment. This constitutes an additional method to

evaluate the effect of the treatment. Therefore, the power of the gamma band may be established as a promising biomarker for assessing the severity of neuropathic pain.

Our study explored the gamma band activity in neuropathic pain patients. The results showed that gamma band activity was decreased under DRGS treatment. However, the knowledge about the mechanism of DRGS treatment has not been comprehensively understood so far. Based on our findings and previous results, we can infer that one of the pain relief mechanisms of DRGS treatment is that it may reduce the hyper excitability of cortical neurons in the central nervous system.

4.4 The role of DRG in the development of neuropathic pain

It is known that DRG is one key structure in the development of neuropathic pain. The DRG is just like a relay station, which can receive noxious signals from the peripheral nociceptors before transmitting them to the central nervous system (CNS). Evidence has shown that the DRG can also enhance the APs after PAF injury (Wu et al., 2002). During this period, the primary sensory neurons of the DRG always manifest abnormal features such as excitement and hypersensitivity (Krames, 2014). The presence of hypersensitivity is due to the decreased threshold of nociceptors which form APs. The activation of abnormal and normal sodium (Na+) channels within the DRG has also contributed to this pathological process.

Besides, the peripheral immune system may also be involved in the development of neuropathic pain. After PAF injury, the immune cascade might be activated. White blood cells, T cells, Schwann cells, glial cells, and other immune-related cells all can participate in this process (Chessell et al., 2005). Activation of these cells promotes the release of various pain mediators. The Schwann cells and glial cells within the DRG can release various cytokines after the damage. Meanwhile, the adjacent cells may be regulated and affected by these cytokines (Turnbull & Rivier, 1999). Many

inflammatory mediators such as bradykinins, serotonin, neurotrophins, and cytokines were released. Some mechanisms of action regarding these mediators have already been revealed (i.e. growth factors, Tumor Necrosis Factor-Alpha (TNF-α), interferons, chemokines) (Wagner & Myers, 1996; White, Bhangoo, & Miller, 2005). They can sensitize neurons and reduce the threshold for AP release before resulting in the sensitization of the peripheral and central nervous system and causing chronic neuropathic pain (Deleo, Tanga, & Tawfik, 2004). There is no doubt that these pro-inflammatory factors promote the development of neuropathic pain.

Among these cytokines, neurotrophic growth factors may have played key roles in the development of neuropathic pain. This kind of mediators, which are closely related to the growth, differentiate and maintain the nervous system. Data have already shown that glial-derived neurotrophic factor (GDNF) has a protective effect on the neuropathic pain process after nerve injury (Macias et al., 2006). As an axon membrane protein, growth-associated protein-43 (GAP-43) which is also known as neuromodulin, participates in the growth of nerve cells, synaptic development and nerve cell regeneration (Murata et al., 2006). Woolf et al. reported that after the peripheral nerve injury in animal models, the increased GAP-43 levels are likely to result in afferent terminals' abnormal synaptic reorganization (Woolf, Reynolds, Molander, O'Brien, & Lindsay, 1990). Besides, other neurotrophic growth factors such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), insulin-like growth factor-I and others may also have vital influences on the development of neuropathic pain (Sah, Porreca, & Ossipov, 2006).

4.5 Primary therapies of neuropathic pain

4.5.1 Pharmacological therapy of neuropathic pain

The medical treatment of neuropathic pain is still one difficult issue in clinical practice. Relieving the pain of patients is a top priority facing pain physicians. Over the past several decades, thanks to the efforts made by clinicians and researchers, the mechanisms of neuropathic pain have been gradually revealed. The revealing of these mechanisms has greatly helped the setting of effective therapeutic targets. Some targeted drugs have been successfully applied to the clinic. In order to help the neurologist work out a better drug treatment strategy, in 2006, the first version of guidelines on pharmacological treatment of neuropathic pain was released by the European Federation of Neurological Societies (EFNS) (Nadine Attal et al., 2006). The EFNS Task Force searched the Cochrane and Medline databases for all Class I and II control trials for pharmacological treatment of neuropathic pain. Multiple painful diseases including common and rare neuropathic pain conditions were classified as individual chapters. The expert panel considered various factors including trial's efficiency, drug's indications and adverse reactions, patient's life quality and other safety issues concerning medical treatment. All recommended drugs were classified as the first line, second line and third line for each pain condition. The effective dosage of the drug is also accurately recommended. For some complex pain conditions, the combination of multiple drugs' therapy is also suggested. These detailed guidelines have greatly helped clinicians present a better therapy strategy for pain patients. In 2010, the guidelines was updated by EFNS Task force (N Attal et al., 2010). More high-quality randomized controlled trials (RCTs) were incorporated into assessment system, making the guidelines more precise.

4.5.2 Interventional therapy of neuropathic pain

In general, interventional therapy was not considered as the first choice for neuropathic pain patients. Physicians usually recommended it to patients when the pharmacological therapy outcomes were not satisfying. However, the recommendation of interventional treatments in clinical trials is not enough because of the lack of evidence of high level trials regarding its safety and efficacy (N Attal et al., 2010). Interventional therapy contains non-invasive and invasive therapies. Transcutaneous electrical nerve stimulation is one of non-invasive interventional therapies for chronic pain disorders (Binder & Baron, 2010). It has been applied in clinical practice for decades. Although the evidence is not strong enough to be recommended in some pain disorders (Dubinsky & Miyasaki, 2010), it may also remain to be considered as one of the treatment options in some pain patients (Giorgio Cruccu et al., 2007).

For invasive therapies, injection therapy (i.e. epidural, facet joint, local site) is the most common form in chronic pain patients. The delivery of a drug can block the peripheral nerves and muscles that interrupt the nociceptive input effect, thus achieving the effect of the pain relief (Turk, Wilson, & Cahana, 2011). This therapy is simple and easy to perform, but there are no systematic research and guidelines about patient selection criteria, injection frequency and timing (Friedly, Nishio, Bishop, & Maynard, 2008). Deep brain stimulation (DBS) can be one option for the treatment of neuropathic pain. Periventricular gray matter (PVG) and sensory thalamus are the key targets for DBS therapy (Owen et al., 2006). But the mechanisms of pain relief by DBS are still unclear. SCS is one of invasive therapies in complex regional pain syndrome (CRPS) and failed back surgery syndrome (FBSS) patients (Giorgio Cruccu et al., 2007). The use of this technique has been proven to relieve pain, improve the quality of life and even help pain patients to be able to go back to work (Taylor, 2006). For some localized peripheral neuropathic pain conditions, DRGS can provide a more precise and higher selective strategy when compared to SCS (Deer et al., 2013). Besides, the access to the DRG is

easier when an invasive procedure is chosen. Therefore, the application of this technique is rapidly expanding in clinical practice.

4.6 Dorsal root ganglion stimulation therapy

There are numerous studies which could demonstrate the multiple beneficial effects of electrical stimulation such as promoting the regeneration of neurons after nerve injury (Ming, Henley, Tessier-Lavigne, Song, & Poo, 2001), enhancing wound healing (Kloth, 2005), and upregulating growth factors (Aaron, Boyan, Ciombor, Schwartz, & Simon, 2004). The release of growth factors in the DRG is also one of the important reasons for reducing neuropathic pain. The synthesis of growth factors could be activated by the electrical stimulation (Aaron et al., 2004). This means that the electrical stimulation of the DRG may decrease the response of the immune system to the nerve injury. It is well known that the normal ion channels are important for the maintenance of APs. After the PAF injury, the abnormal Na+, K+, and Ca++ channel changes could occur within DRG neurons. The electrical stimulation of the DRG can greatly stabilize the neuronal hypersensitivity. The direct electrical stimulation of neurons can increase Ca++ influx into the cell, which down-regulates the neuronal excitability, thereby reducing the generation of APs (Koopmeiners, Mueller, Kramer, & Hogan, 2013). In addition, electrical stimulation of the DRG may also have some functions such as modulating upstream and downstream physiological features (Krames, 2015). It may produce an upstream effect of vasodilation and attenuate the downstream effect of the sensitized neurons. Besides, it may also make sensitized peripheral nociceptors stable and modulate supraspinal brain regions which are related to neuropathic pain.

Based on these previous studies, more and more specific pain conditions are available for DRGS therapy. Phantom limb pain (PLP) is one of the special distinct neuropathic pain conditions. Sam et al. reported the application of DRGS in PLP patients (Eldabe et al., 2015). The average pain ratings of eight subjects dropped from 85.5mm to 43.5mm.

Meanwhile, their quality of life and functional capacity have also improved. Besides, in the therapeutic areas of CPRS, DRGS also showed its superiority. In a prospective study in 2014, eight subjects with CPRS had an average pain reduction of 62% after one month of DRGS therapy (Van Buyten, Smet, Liem, Russo, & Huygen, 2015).

Low back pain is also a well-known pain condition and difficult to treat. About 12% of the population suffers from this disease (Manchikanti, Singh, Falco, Benyamin, & Hirsch, 2014). It was also listed as a first disability according to the research results of the Global Burden of Disease study in 2010(Murray et al., 2012). Failed back surgery syndrome (FBSS) was one cause resulting in low back pain. Although some evidence has proven that traditional SCS can be used to treat low back pain (Rigoard et al., 2011), the limitations of SCS therapy in pain relief are obvious. Due to the special location of the lumbosacral sensory nerve fibers, precise coverage is a huge challenge for SCS (Oakley, 2006). Frank et al. observed effective pain relief in FBSS patients after using DRGS treatment (Huygen, Liem, Cusack, & Kramer, 2018). Meanwhile, the function, mood, and quality of life of patients were also improved.

Compared with traditional SCS, DRGS is a relatively new technique. More and more evidence suggests that this new therapy does have an effective therapeutic effect on a variety of neuropathic pain conditions (Deer et al., 2019). Our study also demonstrated that neuropathic pain patients under DRGS treatment can recover their LEP and that their gamma band power can be reduced. It is believed that the indications for DRGS therapy will rapidly expand and that the therapy will benefit more neuropathic pain patients in the future.

4.7 Limitations of the study

This study also has limitations. Only 9 patients were included in the project because of the strict inclusion criteria. Due to the small number of patients, the statistical power is

weakened. In a subsequent study, more patients will be included, which will increase the power of statistics.

5. Conclusion

In this study, we showed that under the DRGS treatment, the LEP of neuropathic pain patients can recover in 7 days, although the amplitude of N2-P2 wave complex is not as large as that of the healthy volunteer and even not as large as the control side. The DRGS treatment has a lasting rather than temporary effect. Meanwhile, the power of lower gamma band (30-45 Hz) and higher gamma band (55-95 Hz) was reduced after 7 days DRGS treatment. NRS is positively correlated with lower gamma band power and higher gamma band power, respectively. These findings suggest that DRGS not only has a therapeutic effect, it may also be involved in some regulatory processes of chronic neuropathic pain.

6. Summary

Neuropathic pain is a disease that affects about 10 % of the people in the world (Colloca et al., 2017). The management and treatment of chronic neuropathic pain are still very difficult. The underlying causes of this serious pain condition are still only poorly understood.

Shealy (Shealy, Mortimer, & Reswick, 1967) first introduced spinal cord stimulation into the clinical treatment of chronic neuropathic pain (Loeser & Treede, 2008; Moore, 2009) in 1967 and achieved good results. Another new type of dorsal root ganglion stimulation (DRGS) has also become a promising and helpful method to relief chronic neuropathic pain (Deer et al., 2013; Sapunar, Kostic, Banozic, & Puljak, 2012).

Laser evoked potentials (LEP) have proven to be one of the most effective tools for evaluating the integrity of pain pathways. Based on our previous research, we have shown that the LEP recovers in localized chronic neuropathic pain patients under DRGS. Gamma band activation is considered to actively participate in pain processing (Wang et al., 2016). The power of the gamma band has been reported to be significantly increased in patients with neuropathic pain compared with healthy volunteers (Lim et al., 2016). We designed this study specifically in order to investigate the changes in gamma band activity in patients with neuropathic pain receiving DRGS treatment.

In the present study, we set three different adjoining time points to measure the LEP and gamma band power of chronic neuropathic pain patients who were undergoing the treatment of DRGS. We have demonstrated that the LEP of neuropathic pain patients could be restored within 7 days. The NRS of these patients was also decreased when compared to pre-surgery. Meanwhile, the power of lower gamma band (30-45 Hz) and higher gamma band (55-95 Hz) was also reduced after 7 days of DRGS treatment. The

NRS was positively correlated with lower gamma band power and higher gamma band power, respectively.

These findings suggest that DRGS does not only have a therapeutic effect but also may be involved in some regulatory processes of chronic neuropathic pain. The restored LEP and decreased gamma band power offer valuable and more objective neurophysiological evidence for the pain relief after DRGS therapy than the mere subjective pain relief as measured by the NRS pain scale. Therefore, they might be useful as neurophysiological markers for the assessment of the efficacy of a neuro modulatory treatment of chronic neuropathic pain patients. Further studies with more patients will have to be done in order to confirm these results.

7. Zusammenfassung

Neuropathische Schmerzen sind schwierig zu behandeln und stellen häufig ein großes Problem dar. Etwa 10% der Menschen sind weltweit davon betroffen (Colloca et al., 2017). Die Erkrankung nimmt dabei meist einen chronischen Verlauf und schränkt die Lebensqualität der Betroffenen häufig stark ein. Versicherungsträger und die Gesellschaft aber auch die Betroffenen und die Angehörigen sind durch dieses Schmerzsysndrom gleichermaßen massiv beeinträchtigt.

Shealy hat (Shealy et al., 1967) 1967 erstmals die Rückenmarkstimulation in die klinische Behandlung für chronische neuropathische Schmerzen eingeführt (Loeser & Treede, 2008; Moore, 2009) und damit gute Ergebnisse erzielt. Die Dorsalganlienstimulation ist eine neue neuromodulative Stimulationsform, die insbesondere chronische neuropathische Schmerzen in diskreten Schmerzarealen gezielt zu reduzieren vermag. Sie stellt damit eine wichtige Ergänzung zu den bereist bestehenden Stimulationsformen dar (Deer et al., 2013; Sapunar et al., 2012).

Laser evozierte Potenziale (LEP) sind derzeit die effektivste Methode um die Integrität der nozizeptiven Bahnen zu untersuchen und gelten aktuell als Goldstandard um neuropathische Schmerzen zu diagnostizieren. In früheren Untersuchungen konnten wir zeigen, dass sich die LEPs bei Patienten mit lokalen chronischen neuropathischen Schmerzen unter DRGS wieder erholten. Das Gammaband kann zur Beurteilung von Prozessen in der Schmerzverarbeitung genutzt werden (Wang et al., 2016). Es wurde berichtet, dass die Gammabandaktivität bei Patienten mit neuropathischen Schmerzen im Vergleich zu gesunden Probanden signifikant erhöht ist (Lim et al., 2016). Wir haben diese Studie durchgeführt um speziell auch Veränderungen der Gammabandaktivität bei Patienten mit neuropathischen Schmerzen unter DRGs-Behandlungen zu untersuchen.

In der vorliegenden Studie haben wir bei Patienten mit chronischen neuropathischen Schmerzen an drei verschiedenen aufeinanderfolgenden Zeitpunkten LEP- und Gammabanduntersuchungen durchgeführt. Wir konnten zeigen, dass das LEP von neuropathischen Schmerzpatienten innerhalb von 7 Tagen wiederhergestellt werden konnte. Der NRS-Wert der Patienten war im Vergleich zu präoperativ ebenfalls verringert. Gleichzeitig hat die Leistung des unteren Gammabandes (30-45 Hz) und des höheren Gammabandes (55-95 Hz) nach 7 Tagen DRGS-Behandlung ebenfalls abgenommen. Der NRS-Wert korrelierte dabei positiv mit einer niedrigeren bzw. einer höheren Gammabandleistung.

Diese Ergebnisse zeigen, dass die Stimulation des Dorsalganglions auch bei der zentralen Verarbeitung chronischer neuropathischer Schmerzen beteiligt sein kann. Das wiederhergestellte LEP und die verringerte Gammabandleistung bei der DRGS-Therapie können einen wertvolleren und objektiveren neurophysiologischen Beweis für die Schmerzlinderung liefern als nur die bloße subjektive Schmerzlinderung, gemessen anhand der NRS-Schmerzskala. Daher könnten diese Parameter möglicherweise als neurophysiologische Marker für die Beurteilung der Wirksamkeit einer neuromodulativen Behandlung von Patienten mit chronischen neuropathischen Schmerzen genutzt werden. Weitere Studien mit einem größeren Patientenkollektiv sind jedoch notwendig, um diese Ergebnisse zu bestätigen.

8. Bibliography

Aaron, R. K., Boyan, B. D., Ciombor, D. M., Schwartz, Z., & Simon, B. J. (2004). Stimulation of growth factor synthesis by electric and electromagnetic fields. *Clinical Orthopaedics and Related Research (1976-2007), 419*, 30-37.

Agostino, R., Cruccu, G., Iannetti, G., Romaniello, A., Truini, A., & Manfredi, M. (2000). Topographical distribution of pinprick and warmth thresholds to CO2 laser stimulation on the human skin. *Neuroscience letters, 285*(2), 115-118.

Aldskogius, H., Elfvin, L.-G., & Forsman, C. A. (1986). Primary sensory afferents in the inferior mesenteric ganglion and related nerves of the guinea pig: An experimental study with anterogradely transported wheat germ agglutinin-horseradish peroxidase conjugate. *Journal of the autonomic nervous system, 15*(2), 179-190.

Almeida, T. F., Roizenblatt, S., & Tufik, S. (2004). Afferent pain pathways: a neuroanatomical review. *Brain research, 1000*(1-2), 40-56.

Arendt-Nielsen, L., & Chen, A. C. (2003). Lasers and other thermal stimulators for activation of skin nociceptors in humans. *Neurophysiologie Clinique/Clinical Neurophysiology, 33*(6), 259-268.

Attal, N., Cruccu, G., Baron, R. a., Haanpää, M., Hansson, P., Jensen, T. S., & Nurmikko, T. (2010). EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European journal of neurology, 17*(9), 1113-e1188.

Attal, N., Cruccu, G., Haanpää, M., Hansson, P., Jensen, T. S., Nurmikko, T., . . . Wiffen, P. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. *European journal of neurology, 13*(11), 1153-1169.

Baron, R. (2006). Mechanisms of disease: neuropathic pain—a clinical perspective. *Nature Reviews Neurology, 2*(2), 95.

Baron, R., Binder, A., & Wasner, G. (2010). Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology, 9*(8), 807-819.

Bennett, M. I., Attal, N., Backonja, M. M., Baron, R., Bouhassira, D., Freynhagen, R., . . . Jensen, T. S. (2007). Using screening tools to identify neuropathic pain. *Pain, 127*(3), 199-203.

Bevan, S., & Yeats, J. (1991). Protons activate a cation conductance in a sub-population of rat dorsal root ganglion neurones. *The Journal of Physiology, 433*(1), 145-161.

Bhattacharya, J. (2000). Complexity analysis of spontaneous EEG. *Acta neurobiologiae experimentalis, 60*(4), 495-502.

Binder, A., & Baron, R. (2010). Utility of transcutaneous electrical nerve stimulation in neurologic pain disorders. *Neurology, 74*(2), 104-105.

Bromm, B., & Lorenz, J. (1998). Neurophysiological evaluation of pain. *Electroencephalography and clinical neurophysiology, 107*(4), 227-253.

Bromm, B., & Treede, R.-D. (1983). CO 2 laser radiant heat pulses activate C nociceptors in man. *Pflügers Archiv, 399*(2), 155-156.

Bromm, B., & Treede, R.-D. (1987). Human cerebral potentials evoked by CO 2 laser stimuli causing pain. *Experimental brain research, 67*(1), 153-162.

Bromm, B., & Treede, R. (1984). Nerve fibre discharges, cerebral potentials and sensations induced by CO2 laser stimulation. *Human neurobiology, 3*(1), 33-40.

Carmon, A., Dotan, Y., & Sarne, Y. (1978). Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. *Experimental brain research, 33*(3-4), 445-453.

Carmon, A., Mor, J., & Goldberg, J. (1976). Evoked cerebral responses to noxious thermal stimuli in humans. *Experimental brain research, 25*(1), 103-107.

Chatrian, G., Lettich, E., & Nelson, P. (1985). Ten percent electrode system for topographic studies of spontaneous and evoked EEG activities. *American Journal of EEG technology, 25*(2), 83-92.

Chessell, I. P., Hatcher, J. P., Bountra, C., Michel, A. D., Hughes, J. P., Green, P., . . . Peck, W. L. (2005). Disruption of the P2X7 purinoceptor gene abolishes chronic inflammatory and neuropathic pain. *Pain, 114*(3), 386-396.

Cohen, M. S., Wall, E. J., Brown, R. A., Rydevik, B., & Garfin, S. R. (1990). 1990 AcroMed Award in basic science. Cauda equina anatomy. II: Extrathecal nerve roots and dorsal root ganglia. *Spine, 15*(12), 1248-1251.

Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., . . . Raja, S. N. (2017). Neuropathic pain. *Nat Rev Dis Primers, 3*, 17002. doi: 10.1038/nrdp.2017.2

Costigan, M., Scholz, J., & Woolf, C. J. (2009). Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual review of neuroscience, 32*, 1-32.

Cruccu, G., Aziz, T., Garcia-Larrea, L., Hansson, P., Jensen, T. S., Lefaucheur, J. P., . . . Taylor, R. (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. *European journal of neurology, 14*(9), 952-970.

Cruccu, G., Sommer, C., Anand, P., Attal, N., Baron, R., Garcia-Larrea, L., . . . Treede, R. D. (2010). EFNS guidelines on neuropathic pain assessment: revised 2009. *European journal of neurology, 17*(8), 1010-1018.

D'mello, R., & Dickenson, A. (2008). Spinal cord mechanisms of pain. *British journal of anaesthesia, 101*(1), 8-16.

Deer, T. R., Grigsby, E., Weiner, R. L., Wilcosky, B., & Kramer, J. M. (2013). A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation: Technology at the Neural Interface, 16*(1), 67-72.

Deer, T. R., Pope, J. E., Lamer, T. J., Grider, J. S., Provenzano, D., Lubenow, T. R., . . . Sayed, D. (2019). The neuromodulation appropriateness consensus committee on best practices for dorsal root ganglion stimulation. *Neuromodulation: Technology at the Neural Interface, 22*(1), 1-35.

Deleo, J. A., Tanga, F. Y., & Tawfik, V. L. (2004). Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. *The Neuroscientist, 10*(1), 40-52.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods, 134*(1), 9-21.

Devor, M. (1999). Unexplained peculiarities of the dorsal root ganglion. *Pain, 82*, S27-S35.

Dubinsky, R. M., & Miyasaki, J. (2010). Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology, 74*(2), 173-176.

Eklund, A., Montgomery, A., Bergkvist, L., & Rudberg, C. (2010). Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. *British Journal of Surgery, 97*(4), 600-608.

Eldabe, S., Burger, K., Moser, H., Klase, D., Schu, S., Wahlstedt, A., . . . Subbaroyan, J. (2015). Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). *Neuromodulation: Technology at the Neural Interface, 18*(7), 610-617.

Elias, M. (2000). Spinal cord stimulation for post-herniorrhaphy pain. *Neuromodulation: Technology at the Neural Interface, 3*(3), 155-157.

Ergenoglu, T., Demiralp, T., Bayraktaroglu, Z., Ergen, M., Beydagi, H., & Uresin, Y. (2004). Alpha rhythm of the EEG modulates visual detection performance in humans. *Cognitive Brain Research, 20*(3), 376-383.

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L., Bouhassira, D., . . . Nurmikko, T. (2016). Neuropathic pain: an updated grading system for research and clinical practice. *Pain, 157*(8), 1599.

Finnerup, N. B., Scholz, J., Attal, N., Baron, R., Haanpää, M., Hansson, P., . . . Rowbotham, M. (2013). Neuropathic pain needs systematic classification. *European journal of pain, 17*(7), 953-956.

Friedly, J., Nishio, I., Bishop, M. J., & Maynard, C. (2008). The relationship between repeated epidural steroid injections and subsequent opioid use and lumbar surgery. *Archives of physical medicine and rehabilitation, 89*(6), 1011-1015.

Frot, M., Rambaud, L. c., Guénot, M., & Mauguière, F. (1999). Intracortical recordings of early pain-related CO2-laser evoked potentials in the human second somatosensory (SII) area. *Clinical neurophysiology, 110*(1), 133-145.

Gagliese, L., & Melzack, R. (2000). Age differences in nociception and pain behaviours in the rat. *Neuroscience & Biobehavioral Reviews, 24*(8), 843-854.

Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: from dipoles to functional significance. *Neurophysiologie Clinique/Clinical Neurophysiology, 33*(6), 279-292.

Garcia-Larrea, L., Convers, P., Magnin, M., André-Obadia, N., Peyron, R., Laurent, B., & Mauguière, F. (2002). Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. *Brain, 125*(12), 2766-2781.

Gemes, G., Koopmeiners, A., Rigaud, M., Lirk, P., Sapunar, D., Bangaru, M. L., . . . Mueller, S. J. (2013). Failure of action potential propagation in sensory neurons: mechanisms and loss of afferent filtering in C-type units after painful nerve injury. *The Journal of Physiology, 591*(4), 1111-1131.

Gross, J., Schnitzler, A., Timmermann, L., & Ploner, M. (2007). Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS biology, 5*(5), e133.

Haanpää, M., Attal, N., Backonja, M., Baron, R., Bennett, M., Bouhassira, D., . . . Iannetti, G. D. (2011). NeuPSIG guidelines on neuropathic pain assessment. *PAIN®, 152*(1), 14-27.

Haefeli, M., & Elfering, A. (2006). Pain assessment. *European Spine Journal, 15*(1), S17-S24.

Hanani, M. (2005). Satellite glial cells in sensory ganglia: from form to function. *Brain research reviews, 48*(3), 457-476.

Haroutiunian, S., Nikolajsen, L., Finnerup, N. B., & Jensen, T. S. (2013). The neuropathic component in persistent postsurgical pain: a systematic literature review. *PAIN®, 154*(1), 95-102.

Hasegawa, T., An, H. S., & Haughton, V. M. (1993). *Imaging anatomy of the lateral lumbar spinal canal.* Paper presented at the Seminars in Ultrasound, CT and MRI.

Herculano-Houzel, S. (2009). The human brain in numbers: a linearly scaled-up primate brain. *Frontiers in human neuroscience, 3*, 31.

Hogan, Q. (2010). Labat lecture: the primary sensory neuron: where it is, what it does, and why it matters. *Regional anesthesia and pain medicine, 35*(3), 306.

Hu, L., Xiao, P., Zhang, Z., Mouraux, A., & Iannetti, G. D. (2014). Single-trial time–frequency analysis of electrocortical signals: Baseline correction and beyond. *Neuroimage, 84*, 876-887.

Huygen, F., Liem, L., Cusack, W., & Kramer, J. (2018). Stimulation of the L2–L3 Dorsal Root Ganglia Induces Effective Pain Relief in the Low Back. *Pain Practice, 18*(2), 205-213.

Jasper, H. (1958). Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalogr Clin Neurophysiol, 10*, 370-375.

Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S., & Treede, R.-D. (2011). A new definition of neuropathic pain. *Pain, 152*(10), 2204-2205.

Kakigi, R., Shibasaki, H., & Ikeda, A. (1989). Pain-related somatosensory evoked potentials following CO2 laser stimulation in man. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 74*(2), 139-146.

Kenton, B., Coger, R., Crue, B., Pinsky, J., Friedman, Y., & Carmon, A. (1980). Peripheral fiber correlates to noxious thermal stimulation in humans. *Neuroscience letters, 17*(3), 301-306.

Kikuchi, S., Sato, K., Konno, S., & Hasue, M. (1994). Anatomic and radiographic study of dorsal root ganglia. *Spine, 19*(1), 6-11.

Kishi, M., Tanabe, J., Schmelzer, J. D., & Low, P. A. (2002). Morphometry of dorsal root ganglion in chronic experimental diabetic neuropathy. *Diabetes, 51*(3), 819-824.

Klem, G. H., Lüders, H. O., Jasper, H., & Elger, C. (1999). The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol, 52*(3), 3-6.

Kloth, L. C. (2005). Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. *The international journal of lower extremity wounds, 4*(1), 23-44.

Koopmeiners, A. S., Mueller, S., Kramer, J., & Hogan, Q. H. (2013). Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation: Technology at the Neural Interface, 16*(4), 304-311.

Krames, E. S. (2014). The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Medicine, 15*(10), 1669-1685.

Krames, E. S. (2015). The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. *Neuromodulation: Technology at the Neural Interface, 18*(1), 24-32.

Kumar, J. S., & Bhuvaneswari, P. (2012). Analysis of Electroencephalography (EEG) signals and its categorization–a study. *Procedia engineering, 38*, 2525-2536.

Kunde, V., & Treede, R.-D. (1993). Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 88*(4), 280-289.

Lab, T. M. P. V. (Access data Feburary 04, 2020). 10/20 System of electrode placement.

Lauria, G., Holland, N., Hauer, P., Cornblath, D. R., Griffin, J. W., & McArthur, J. C. (1999). Epidermal innervation: changes with aging, topographic location, and in sensory neuropathy. *Journal of the neurological sciences, 164*(2), 172-178.

Li, L., Liu, X., Cai, C., Yang, Y., Li, D., Xiao, L., . . . Qiu, Y. (2016). Changes of gamma-band oscillatory activity to tonic muscle pain. *Neuroscience letters, 627*, 126-131.

Li, S., Hong, B., Gao, X., Wang, Y., & Gao, S. (2011). Event-related spectral perturbation induced by action-related sound. *Neuroscience letters, 491*(3), 165-167.

Liem, L., Russo, M., Huygen, F. J., Van Buyten, J. P., Smet, I., Verrills, P., . . . Deer, T. (2013). A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation: Technology at the Neural Interface, 16*(5), 471-482.

Lim, M., Kim, J. S., Kim, D. J., & Chung, C. K. (2016). Increased low-and high-frequency oscillatory activity in the prefrontal cortex of fibromyalgia patients. *Frontiers in human neuroscience, 10*, 111.

Loeser, J. D., & Treede, R.-D. (2008). The Kyoto protocol of IASP Basic Pain Terminology☆. *Pain, 137*(3), 473-477.

Macias, M. Y., Syring, M. B., Pizzi, M. A., Crowe, M. J., Alexanian, A. R., & Kurpad, S. N. (2006). Pain with no gain: allodynia following neural stem cell transplantation in spinal cord injury. *Experimental neurology, 201*(2), 335-348.

Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in cognitive sciences, 8*(5), 204-210.

Makeig, S., Westerfield, M., Jung, T.-P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science, 295*(5555), 690-694.

Manchikanti, L., Singh, V., Falco, F. J., Benyamin, R. M., & Hirsch, J. A. (2014). Epidemiology of low back pain in adults. *Neuromodulation: Technology at the Neural Interface, 17*, 3-10.

Merskey, H., & Bogduk, N. (1994). Classification of chronic pain, IASP Task Force on Taxonomy. *Seattle, WA: International Association for the Study of Pain Press (Also available online at www. iasp-painorg)*.

Millan, M. J. (1999). The induction of pain: an integrative review. *Progress in neurobiology, 57*(1), 1-164.

Miller, R. (2007). Theory of the normal waking EEG: from single neurones to waveforms in the alpha, beta and gamma frequency ranges. *International journal of psychophysiology, 64*(1), 18-23.

Ming, G.-l., Henley, J., Tessier-Lavigne, M., Song, H.-j., & Poo, M.-m. (2001). Electrical activity modulates growth cone guidance by diffusible factors. *Neuron, 29*(2), 441-452.

Moore, N. D. (2009). In search of an ideal analgesic for common acute pain. *Acute Pain, 11*(3-4), 129-137.

Mor, J., & Carmon, A. (1975). Laser emitted radiant heat for pain research. *Pain, 1*(3), 233-237.

Morgalla, M. H., Bolat, A., Fortunato, M., Lepski, G., & Chander, B. S. (2017). Dorsal Root Ganglion Stimulation Used for the Treatment of Chronic Neuropathic Pain in the Groin: A Single-Center Study With Long-Term Prospective Results in 34 Cases. *Neuromodulation: Technology at the Neural Interface, 20*(8), 753-760.

Morgalla, M. H., de Barros Filho, M. F., Chander, B. S., Soekadar, S. R., Tatagiba, M., & Lepski, G. (2019). Neurophysiological Effects of Dorsal Root Ganglion Stimulation (DRGS) in Pain Processing at the Cortical Level. *Neuromodulation: Technology at the Neural Interface, 22*(1), 36-43.

Murata, R., Ohtori, S., Ochiai, N., Takahashi, N., Saisu, T., Moriya, H., . . . Wada, Y. (2006). Extracorporeal shockwaves induce the expression of ATF3 and GAP-43 in rat dorsal root ganglion neurons. *Autonomic Neuroscience, 128*(1-2), 96-100.

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., . . . Abdalla, S. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet, 380*(9859), 2197-2223.

Nuwer, M. R., Comi, G., Emerson, R., Fuglsang-Frederiksen, A., Guérit, J.-M., Hinrichs, H., . . . Rappelsburger, P. (1998). IFCN standards for digital recording of clinical EEG. *Electroencephalography and clinical neurophysiology, 106*(3), 259-261.

Oakley, J. C. (2006). Spinal cord stimulation in axial low back pain: solving the dilemma. *Pain Medicine, 7*(suppl_1), S58-S63.

Oostenveld, R., & Praamstra, P. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clinical neurophysiology, 112*(4), 713-719.

Organization, W. H. (2004). *International statistical classification of diseases and related health problems* (Vol. 1): World Health Organization.

Owen, S. L., Green, A. L., Nandi, D., Bittar, R. G., Wang, S., & Aziz, T. Z. (2006). Deep brain stimulation for neuropathic pain. *Neuromodulation: Technology at the Neural Interface, 9*(2), 100-106.

Ploner, M., Gross, J., Timmermann, L., Pollok, B., & Schnitzler, A. (2006). Oscillatory activity reflects the excitability of the human somatosensory system. *Neuroimage, 32*(3), 1231-1236.

Ploner, M., Sorg, C., & Gross, J. (2017). Brain rhythms of pain. *Trends in cognitive sciences, 21*(2), 100-110.

Quante, M., Lorenz, J., & Hauck, M. (2010). Laser-evoked potentials: prognostic relevance of pain pathway defects in patients with acute radiculopathy. *European Spine Journal, 19*(2), 270-278.

Rangaswamy, M., Porjesz, B., Chorlian, D. B., Wang, K., Jones, K. A., Bauer, L. O., . . . Reich, T. (2002). Beta power in the EEG of alcoholics. *Biological psychiatry, 52*(8), 831-842.

Rashid, M. H., Inoue, M., Matsumoto, M., & Ueda, H. (2004). Switching of bradykinin-mediated nociception following partial sciatic nerve injury in mice. *Journal of Pharmacology and Experimental Therapeutics, 308*(3), 1158-1164.

Rigoard, P., Delmotte, A., D'Houtaud, S., Misbert, L., Diallo, B., Roy-Moreau, A., . . . Bataille, B. (2011). Back pain: a real target for spinal cord stimulation? *Neurosurgery, 70*(3), 574-585.

Roach, B. J., & Mathalon, D. H. (2008). Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophrenia bulletin, 34*(5), 907-926.

Romaniello, A., Arendt-Nielsen, L., Cruccu, G., & Svensson, P. (2002). Modulation of trigeminal laser evoked potentials and laser silent periods by homotopical experimental pain. *Pain, 98*(1-2), 217-228.

Romaniello, A., Cruccu, G., Frisardi, G., Arendt-Nielsen, L., & Svensson, P. (2003). Assessment of nociceptive trigeminal pathways by laser-evoked potentials and

laser silent periods in patients with painful temporomandibular disorders. *PAIN®, 103*(1-2), 31-39.

Saby, J. N., & Marshall, P. J. (2012). The utility of EEG band power analysis in the study of infancy and early childhood. *Developmental neuropsychology, 37*(3), 253-273.

Sah, D. Y., Porreca, F., & Ossipov, M. H. (2006). Modulation of neurotrophic growth factors as a therapeutic strategy for neuropathic pain. *Drug development research, 67*(4), 389-403.

Salinas, E., & Sejnowski, T. J. (2001). Correlated neuronal activity and the flow of neural information. *Nature reviews neuroscience, 2*(8), 539.

Sapunar, D., Kostic, S., Banozic, A., & Puljak, L. (2012). Dorsal root ganglion–a potential new therapeutic target for neuropathic pain. *Journal of pain research, 5*, 31.

Scholz, J., Finnerup, N. B., Attal, N., Aziz, Q., Baron, R., Bennett, M. I., . . . Davis, K. D. (2019). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain, 160*(1), 53-59.

Schu, S., Gulve, A., ElDabe, S., Baranidharan, G., Wolf, K., Demmel, W., . . . Jahnichen, G. (2015). Spinal cord stimulation of the dorsal root ganglion for groin pain—a retrospective review. *Pain Practice, 15*(4), 293-299.

Schulz, E., May, E. S., Postorino, M., Tiemann, L., Nickel, M. M., Witkovsky, V., . . . Ploner, M. (2015). Prefrontal gamma oscillations encode tonic pain in humans. *Cerebral cortex, 25*(11), 4407-4414.

Shaker, M. M. (2006). EEG waves classifier using wavelet transform and Fourier transform. *Brain, 2*, 3.

Shealy, C. N., Mortimer, J., & Reswick, J. (1967). Electrical inhibition of pain by stimulation of the dorsal columns. *Anesth Analg, 46*(4), 489-491.

Siedenberg, R., & Treede, R.-D. (1996). Laser-evoked potentials: exogenous and endogenous components. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 100*(3), 240-249.

Suarez, E., Viegas, M., Adjouadi, M., & Barreto, A. (2000). Relating induced changes in EEG signals to orientation of visual stimuli using the ESI-256 machine. *Biomedical sciences instrumentation, 36*, 33-38.

Taylor, R. S. (2006). Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. *Journal of pain and symptom management, 31*(4), S13-S19.

Tebano, M., Cameroni, M., Gallozzi, G., Loizzo, A., Palazzino, G., Pezzini, G., & Ricci, G. (1988). EEG spectral analysis after minor head injury in man. *Electroencephalography and clinical neurophysiology, 70*(2), 185-189.

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review, 2*(2), 1-11.

Tiemann, L., Schulz, E., Gross, J., & Ploner, M. (2010). Gamma oscillations as a neuronal correlate of the attentional effects of pain. *Pain, 150*(2), 302-308.

Todd, A. (2002). Anatomy of primary afferents and projection neurones in the rat spinal dorsal horn with particular emphasis on substance P and the neurokinin 1 receptor. *Experimental physiology, 87*(2), 245-249.

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron, 55*(3), 377-391.

Treede, R.-D. (2003). Neurophysiological studies of pain pathways in peripheral and central nervous system disorders. *Journal of neurology, 250*(10), 1152-1161.

Treede, R.-D., Jensen, T. S., Campbell, J., Cruccu, G., Dostrovsky, J., Griffin, J., . . . Serra, J. (2008). Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology, 70*(18), 1630-1635.

Treede, R.-D., Kief, S., Hölzer, T., & Bromm, B. (1988). Late somatosensory evoked cerebral potentials in response to cutaneous heat stimuli. *Electroencephalography and clinical neurophysiology, 70*(5), 429-441.

Treede, R.-D., Lankers, J., Frieling, A., Zangemeister, W., Kunze, K., & Bromm, B. (1991). Cerebral potentials evoked by painful laser stimuli in patients with syringomyelia. *Brain, 114*(4), 1595-1607.

Truini, A., Galeotti, F., Romaniello, A., Virtuoso, M., Iannetti, G., & Cruccu, G. (2005). Laser-evoked potentials: normative values. *Clinical neurophysiology, 116*(4), 821-826.

Truini, A., Haanpää, M., Zucchi, R., Galeotti, F., Iannetti, G., Romaniello, A., & Cruccu, G. (2003). Laser-evoked potentials in post-herpetic neuralgia. *Clinical neurophysiology, 114*(4), 702-709.

Truini, A., Panuccio, G., Galeotti, F., Maluccio, M., Sartucci, F., Avoli, M., & Cruccu, G. (2010). Laser-evoked potentials as a tool for assessing the efficacy of antinociceptive drugs. *European journal of pain, 14*(2), 222-225.

Turk, D. C., Wilson, H. D., & Cahana, A. (2011). Treatment of chronic non-cancer pain. *The lancet, 377*(9784), 2226-2235.

Turnbull, A. V., & Rivier, C. L. (1999). Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiological reviews, 79*(1), 1-71.

Uglem, M., Omland, P. M., Stjern, M., Gravdahl, G. B., & Sand, T. (2017). Habituation of laser-evoked potentials by migraine phase: a blinded longitudinal study. *The journal of headache and pain, 18*(1), 100.

Van Buyten, J. P., Smet, I., Liem, L., Russo, M., & Huygen, F. (2015). Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Practice, 15*(3), 208-216.

Wager, T. D., Matre, D., & Casey, K. L. (2006). Placebo effects in laser-evoked pain potentials. *Brain, behavior, and immunity, 20*(3), 219-230.

Wagner, R., & Myers, R. R. (1996). Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. *Neuroreport, 7*(18), 2897-2901.

Wang, J., Xing, G.-G., Li, X., & Wan, Y. (2016). Enhanced gamma oscillatory activity in rats with chronic inflammatory pain. *Frontiers in neuroscience, 10*, 489.

White, F. A., Bhangoo, S. K., & Miller, R. J. (2005). Chemokines: integrators of pain and inflammation. *Nature reviews Drug discovery, 4*(10), 834.

Woolf, C., Reynolds, M., Molander, C., O'Brien, C., & Lindsay, R. (1990). The growth-associated protein GAP-43 appears in dorsal root ganglion cells and in the dorsal horn of the rat spinal cord following peripheral nerve injury. *Neuroscience, 34*(2), 465-478.

Wright, R. E., & Colliton, J. W. (1995). Neurostimulation of the L2 dorsal root ganglion for intractable disc pain: description of a novel technique. *Neurosurgery, 36*(6), 1101-1110.

Wu, G., Ringkamp, M., Murinson, B. B., Pogatzki, E. M., Hartke, T. V., Weerahandi, H. M., . . . Meyer, R. A. (2002). Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. *Journal of Neuroscience, 22*(17), 7746-7753.

Yakovlev, A. E., Al Tamimi, M., Barolat, G., Karasev, S. A., Merkulov, Y. A., Resch, B. E., & Yakovleva, V. E. (2010). Spinal cord stimulation as alternative treatment for chronic post-herniorrhaphy pain. *Neuromodulation: Technology at the Neural Interface, 13*(4), 288-291.

Zhou, R., Wang, J., Qi, W., Liu, F.-Y., Yi, M., Guo, H., & Wan, Y. (2018). Elevated resting state gamma oscillatory activities in electroencephalogram of patients with post-herpetic neuralgia. *Frontiers in neuroscience, 12*, 750.

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9. List of Figures and Tables

10. Declaration of Contributions to the Dissertation

The dissertation work was carried out at the Neurosurgery department of University Hospital in Tübingen - under the supervision of Prof. Dr. Matthias. H. Morgalla.

The study was designed in collaboration with Prof. Dr. Matthias. H. Morgalla and Dr. Bankim S. Chander.

After being trained by laboratory member Dr. Bankim S. Chander, I carried out all experiments with the assistance of Dr. Bankim S. Chander.

Statistical analysis was carried out independently by myself.

I confirm that I wrote the manuscript myself and that any additional sources of information have been duly cited.

Signature

05.03.2020 in Tübingen

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