Chronic Pain Alters Somatosensory Evoked Potentials and Paired-pulse Inhibition in Athlete

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Abstract

Injuries are inevitable for athletes, and when injuries end up causing chronic pain, they usually force athletes to withdraw from training. Chronic pain is known to be caused by plastic changes in the brain; thus, the purpose of this study was to assess the somatosensory evoked potential (SEP) and the paired-pulse inhibition (PPI) in athletes suffering from chronic pain as compared to pain-free athletes. Twenty track and field (T&F) athletes, that were also undergraduate students, were recruited for this study. These athletes (12 men; 8 women) were divided into two groups of 10 based on their self-reporting of actively experiencing chronic pain (defined as pain that persisted for more than 3 months) or not. Both SEP and PPI in the primary somatosensory cortex (SI) were elicited by constant current square-wave pulses (of 0.2 ms duration) that were delivered to the right median nerve by an electrical stimulator through a surface bar electrode with a cathode proximal. Paired-pulse stimulation was set at interstimulus intervals of 30 and 100 ms. Subjects were randomly presented with 1,500 single- and paired-pulse stimuli at 2 Hz. Our measurements demonstrated a trend toward a lower N20 and P25 amplitude as well as a disinhibition of the PPI_30 ms in the athletes suffering from chronic pain. These findings suggest that chronic pain may modulate excitatory and inhibitory function of the SI in athletes as well as in patients suffering from complex regional pain syndrome or fibromyalgia.

Introduction

Athletes push themselves physically and mentally in order to achieve high performance. It is, thus, not uncommon for them get injured as it is not uncommon for them to continue to compete while suffering from chronic pain. Chronic pain is caused by a complex combination of factors, including plastic changes in the central nervous system, psychological factors, and social factors[1]; all of them are known to exacerbate the experienced pain. Therefore, it is very difficult to identify the causes of chronic pain in athletes.

In this study, we decided to examine the neurophysiological aspects of chronic pain in athlete, in which the sensation of pain is known not to be affected by cognitive states such as psychological conditions and attention. We employed the somatosensory evoked potential (SEP), which is a method capable of measuring the sensory function in human. When the median nerve is stimulated at the wrist joint, a component called N20 appears, and this N20 is considered to be an indicator of the excitability of the primary somatosensory cortex (SI), at the area 3b[2-4]. On the other hand, the paired-pulse inhibition (PPI) is known as an indicator of the inhibitory function of the SI. Lenz et al. (2011) have evaluated the excitability of the SI by a single-pulse median nerve stimulation, as well as the inhibitory function of a paired-pulse median nerve stimulation, with an interstimulus interval (ISI) of 30 ms, in patients with complex regional pain syndrome (CRPS); a form of chronic pain. Their findings have shown that CRPS patients exhibit a significant decrease in N20 and PPI as compared to the healthy control group[5]. Lim et al. (2015) have also employed magnetoencephalography in order to assess the inhibitory function of the SI in patients with fibromyalgia during two consecutive median nerve stimulations with an ISI of 100 ms.

The results showed that the PPI of the SI was weakened in patients with fibromyalgia as compared to the healthy control group, suggesting that plastic changes may occur in the SI of patients with chronic pain[6].

Cortical plastic changes have been shown to be related to the intensity of CRPS pain, and that when CRPS pain is reduced as a result of treatment, the cortical plastic changes also return to normal[7]. Moreover, it has been reported that cortical plastic changes are associated with the onset, maintenance and improvement of chronic pain[8]. In other words, plastic changes occur in the SI of patients suffering from chronic pain, and these changes may affect the excitability and inhibitory functions in SI. Therefore, the purpose of this study was to assess the nature of chronic pain (from a neurophysiological perspective, by employing SEP and PPI) in athletes. We hypothesized that the SI in athletes suffering from chronic pain would demonstrate a decrease in its SEP and a reduction of its PPI (as compared to pain-free athletes), in the same way the SI of chronic pain patients (suffering from CRPS or fibromyalgia) would.

Methods

Subjects

Twenty track and field (T&F) athletes, that were also undergraduate students, were recruited for this study. Written informed consent was obtained from each of the participating athletes after a full explanation of the study's objectives and methodology. The athletes (12 men; 8 women) were then divided into two groups of 10 based on their self-reporting of actively experiencing chronic pain (8 men; 2 women, age 19.9 ± 0.6 years, height 172 ± 5.9) or not (4men; 6 women, age 19.9 ± 0.9 years, height 163 ± 8.3). Chronic pain was defined as pain that persisted for more than 3 months[9]. The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of the Niigata University of Health and Welfare, Niigata, Japan.

SEP and PPI recording

Electroencephalographic (EEG) signals were recorded at a sampling rate of 5000 Hz by using a Brain Products amplifier system (Brain Products Gmbh, Gilching, Germany). The active electrode was placed at C3' (located 2 cm posterior from C3), the reference electrode was placed over Fz, and the ground electrode placed on Fp2. SEP and PPI assessed the excitability and inhibitory function in the SI, respectively. SEP and PPI were elicited by constant current square-wave pulses (of 0.2 ms duration) delivered to the right median nerve with an electrical stimulator through a surface bar electrode, with a cathode proximal. Stimulus intensity was set at 250% of the sensory threshold[10,11]. PPI was set at an ISI of 30 and of 100 ms[11,12]. Subjects were randomly presented with 1,500 single- and paired-pulse stimuli at 2 Hz by the pulse control system (Pulse Timer II; Medical Try System, Tokyo, Japan) and were asked not to pay attention to the stimulated hand. Continuous EEG data were obtained through a band-pass filter set at 3–2000 Hz, and the filtered data were then restricted to those obtained 20 ms before the induction of the

stimulus, up until (and including) those obtained 200 ms after the induction of the stimulus. Epochs with a response exceeding ±70μV were rejected from the data, and the remaining data were averaged.

Analyses

The peak amplitudes of N20 and P25 were measured relatively to the pre-stimulus baseline from -20 ms to 0 ms at the C3' electrode between 10–20 ms and 20–30 ms after the stimulus onset, respectively, in the single-pulse SEP. In the paired-pulse SEP, the response following the second response was obtained by subtracting the single-pulse SEP waveform in order to assess the "true" paired-pulse interaction. The PPI values at 30 and 100 ms were calculated as the ratio between the first response of the paired pulse and the second response of the subtracted paired pulse, in accordance with previous studies[5,10,11].

The Shapiro–Wilk test was performed in order to confirm the normal distribution prior to the statistical analysis using GraphPad Prism v 9.1.0 (San Diego, CA, USA). If the data were confirmed to be normally distributed, then the Welch's t-test was performed; if not, then the Mann–Whitney's test was performed. Differences in the amplitudes of N20, P25 and in the PPI ratios were also assessed in the two athlete groups (pain-free athletes versus athletes suffering from chronic pain). The statistical significance was set at $p < 0.05$ for all tests. The Cohen's d test was also applied for the assessment of the effect size that the number of the recruited athletes might have on the validity of the study.

Results

Amplitude of N20 and P25

Figure 1 presents the grand-averaged waveform for a single and median nerve stimulation at the C3' electrode position for the two athlete groups. The amplitude of N20 tended to be lower in the chronic pain athlete group than in the pain-free athlete group (-1.55 ± 0.48 vs -2.88 ± 1.96 μV, t(10.11) = 2.069, p = 0.065, d = 0.93) (Fig 2A). On the other hand, there was no group difference observed with regard to the amplitude of P25 (2.11 ± 1.28 vs 3.02 ± 1.6 μV, p = 0.217, d = 0.64) (Fig 2B).

PPI at 30 ms and 100 ms

Figures 3 and 4 present the grand-averaged and subtracted waveforms of the somatosensory 30_ms- and PPI_100 ms at the C3' electrode position for the two athlete groups. In the athletes suffering from chronic pain, the somatosensory PPI_30 ms tended to be that of a disinhibition, as compared to that of the pain-free athletes (1.07 ± 0.31 vs 0.88 ± 0.19, t(14.88) = 1.687, p = 0.113, d = 0.74) (Fig 5A). On the other hand, the PPI_100 ms was not significantly different between the two athlete groups (1.21 ± 0.14 vs 1.26 ± 0.21, t(15.76) = 0.608, p = 0.552, d = 0.28) (Fig 5B). The effect size analysis has also revealed a limited or an absence of an effect as a result of the groups' size.

Discussion

In the present study, we compared the SEP and the PPI between pain-free T&F athletes and T&F athletes suffering from chronic pain, in order to examine whether chronic pain induces neuroplastic changes in the somatosensory excitatory and inhibitory function in SI. Our findings have shown that: (i) the N20 amplitudes in the athletes suffering from chronic pain tended to be smaller than those of the pain-free athletes (with a large effect size), (ii) the P25 amplitudes in the athletes suffering from chronic pain tended to be smaller than those of the pain-free athletes (with a mild effect size), as well as (iii) there was a disinhibition trend for the PPI_30 ms in the group of the athletes suffering from chronic pain as compared to the pain-free athlete group (with a mild effect size), while no such trend was observed with regards to the PPI_100 ms. These findings suggest that chronic pain may modulate the excitability of the SI in athletes as well as in chronic pain patients (suffering from CRPS and fibromyalgia).

Decreasing the N20 amplitude in athletes suffering from chronic pain

Our results have shown that the N20 amplitude in the athletes suffering from chronic pain was decreased as compared to the pain-free athletes. Numerous SEP[2-4] and somatosensory evoked field (SEF)[13-15] topographies have indicated that the N20 and the N20m both represent summated excitatory postsynaptic potentials in the area 3b pyramidal neurons, as these are excited at their basal dendrites through specific thalamocortical afferents. In a previous study[5], the excitability of the SI was examined in healthy subjects, non-neuropathic pain control patients, and CRPS patients. The results revealed no significant differences in the N20-P25 amplitude between the CRPS and the non-neuropathic control patients. However, when the healthy subject group was compared with those of the CRPS patients and the non-neuropathic pain control patients, the N20-P25 amplitude in both the CRPS patients and the control patients tended to decrease[5]. The present study has also shown that the N20 amplitude was decreased in the athletes suffering from chronic pain as compared to the pain-free athletes. We speculate that the reason behind the attenuation of the N20 amplitude in the SI is due to thalamic activity. In fact, it has been reported that the thalamic activity is reduced in chronic pain patients [16,17]. This decrease in the thalamic activity suggests that a chronic nociceptive input might have activated the inhibitory system and, thus, suppressed the thalamic function. Iadarola et al. (1995) have suggested that an enhancement of these inhibitory effects might be due to the pre-synaptically increasing GABA production or the post-synaptically increasing of the number of GABA receptors, or both. In other words, the attenuation of the N20 amplitude in chronic pain athletes may be due to an attenuated thalamic activity as a result of strong thalamic inhibition aiming to suppress the pain signal.

Decreasing the P25 amplitude in athletes suffering from chronic pain

Our results have shown that the P25 amplitude in athletes suffering from chronic pain tended to be small compared to that in pain-free athletes, with mild effect size. The functional significance of P25 is still under debate. Wilkström et al. (1996) have investigated the effect of ISI on SEFs through a right median nerve stimulation with an ISI of 0.15, 0.3, 1, 3, and 5 s. The obtained results have shown that the N20m (N20) amplitude was stable between the ISIs of 0.3 and 5s, while the P35m (P25) amplitude was very sensitive to the ISI changes at 0.15, 0.3, and 1 s. Wilkström *et al*. (1996) suggested that the sensitivity of the inhibitory postsynaptic potentials (IPSPs) to short ISIs is strikingly similar to the ISI dependence of the P35m. The source is attributed to soma-near IPSPs that result from a thalamocortical excitation of inhibitory interneurons. Moreover, Huttunen et al. (2008) have attempted to shed more light on the physiology underling the production of the single-pulse- and the paired-pulse-SEFs by means of a pharmacological manipulation with the $GABA_A$ agonist lorazepam. The authors have reported a group difference in the waveform of P35m that was obtained by subtracting the response under lorazepam from that under placebo, in the single-pulse condition. Their suggestion regarding the aforementioned change was that if the hyperpolarization-induced occlusion of the IPSPs occurs as a consequence of lorazepam administration, then this difference in the recorded waveform could be expected to reveal the population IPSP that was reduced as a result of the administered lorazepam[18]. Therefore, the trend of attenuation of the P25 amplitude in the present study might reflect strong inhibitory effects of the IPSP, such as occlusion, in the same way as obtained in a previous study by the lorazepam administration.

Disinhibition of the PPI_30 ms in the athletes suffering from chronic pains

Phenomena of disinhibition of PPI_30 ms in the SI were observed in the athletes suffering from chronic pain. This finding was consistent with that of previous studies. Lenz et al. (2011) have also demonstrated a bilateral somatosensory cortex disinhibition in patients with CRPS, as compared to control patients and healthy subjects. They speculated the occurrence of a bilateral reduction of the GABA-related sensory-motor cortical inhibition or the occurrence of an enhancement of the NMDA-dependent excitatory mechanisms, or both. Therefore, Stude et al. (2016) have attempted to explore the influence of the $GABA_A$ agonist lorazepam on PPI in the SI. Their results have shown that the PPI was significantly reduced as a result of the lorazepam administration and, as a result, they suggested that lorazepam most likely enhances the inhibition of interneurons within the cortical network responsible for generating the PPI, leading to a reduced inhibitory drive, with a subsequently reduced degree of suppression[19]. In fact, Foerster et al. (2012) have proved that the GABA concentration in the right anterior insula was significantly lower in fibromyalgia patients when compared to that of healthy controls, while there was also a trend toward an increased GABA concentration in the anterior cingulate of fibromyalgia patients as compared to that of healthy controls. They also suggested that the diminished inhibitory neurotransmission resulting from the observed lower GABA concentrations within the right anterior insula may play a role in the pathophysiology of fibromyalgia and other central pain syndromes. At the same time, this finding may also suggest a site-specificity for the effects of these GABA concentration-related

fluctuations[20]. Interestingly, Stagg et al. (2009) have shown that the anodal transcranial direct-current stimulation induces a local reduction of GABA levels, while the cathode stimulation causes a reduced glutamatergic neuronal activity that is highly correlated with the observed depletion of GABA[21]. As a result, one could assume that the human neurotransmitter levels can be modified relatively easily. Thus, in the near future, we may be able to control chronic pain in athletes using non-invasive brain stimulation methods. Since we did not measure the actual GABA concentrations in the SI, we are not able to demonstrate whether the GABA levels increased or decreased in the athletes' SI. However, one cannot exclude that the SI of the athletes suffering from chronic pain might be subject to an abnormal modulation of their GABAergic activity.

No modulation of the PPI_100 ms in the athletes suffering from chronic pains

PPI_100 ms did not change for the two athlete groups. The mechanism of PPI with long ISI (i.e. 100 ms) remains unknown. We speculated that the PPI induced with longer ISI reflect a completely different neural pathway and function from that with shorter ISI (i.e. 30 ms). Present results could not mention the mechanism of PPI_100 ms, but chronic pain may not modulate inhibitory networks at PPI_100 ms of the SI in athletes.

Conclusion

Our findings have shown that the decrease in N20 and P25 amplitudes and disinhibition trend for the PPI_30 ms in the athletes suffering from chronic pain. These findings suggest that chronic pain may modulate the excitability and inhibitory fumction of the SI in athletes as well as in chronic pain patients (suffering from CRPS and fibromyalgia).

Declarations

Funding

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Author contribution

Edited the manuscript: KY DS GO HO NO. Conceived and designed the experiments: KY DS. Performed the experiments: KY KS KI YB. Analyzed the data: KY KS. Contributed reagents/materials/analysis tools: KY DS TF HO. Wrote the paper: KY

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Figures

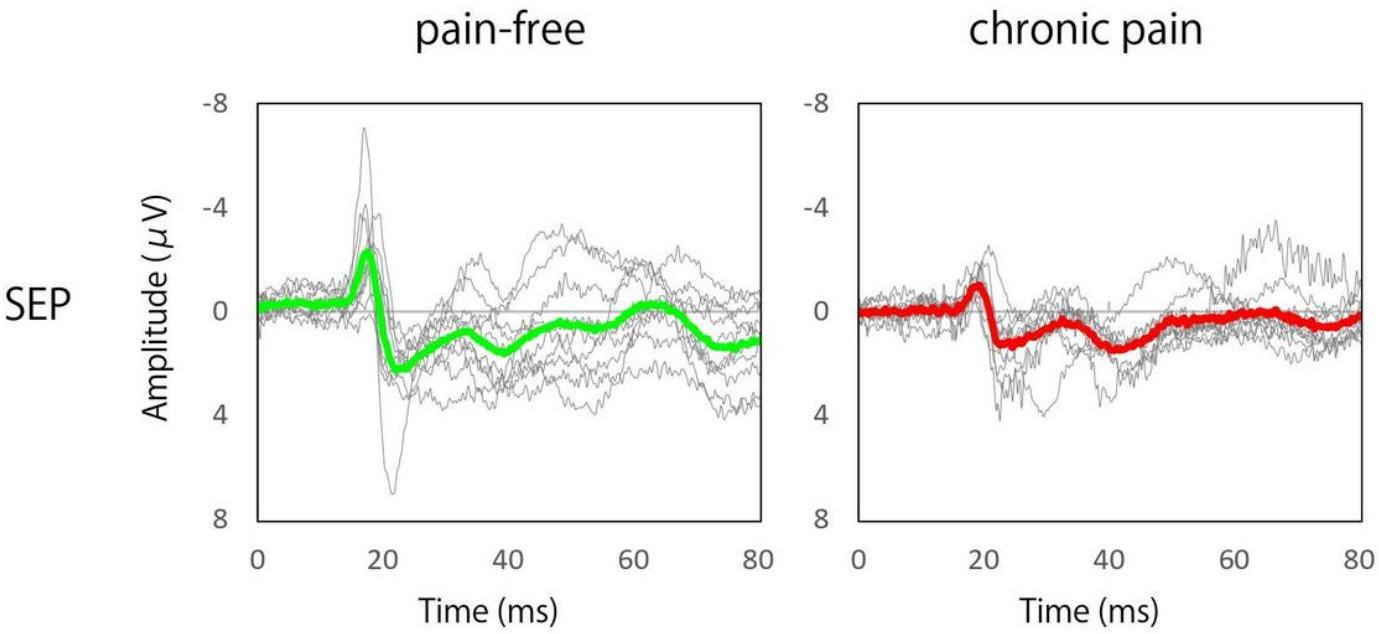

Figure 1

Grand averaged SEP waveforms in pain-free and chronic pain athlete groups. Green and Red thick line show grand averaged waveforms pain-free and chronic pain athlete groups, respectively. Gray thin line shows individual waveforms.

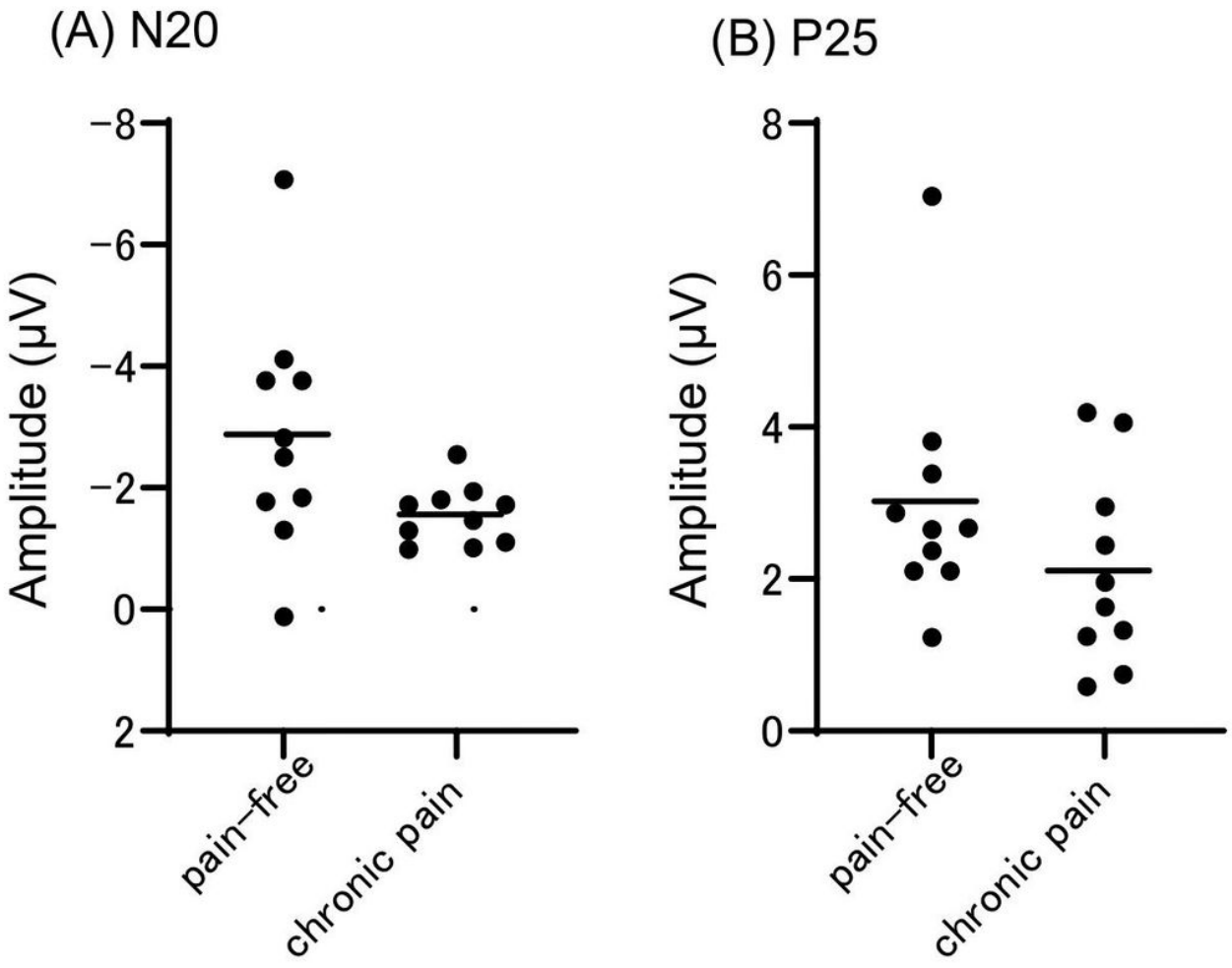

Figure 2

The peak amplitude of N20 and P25 are extracted for each subjects.

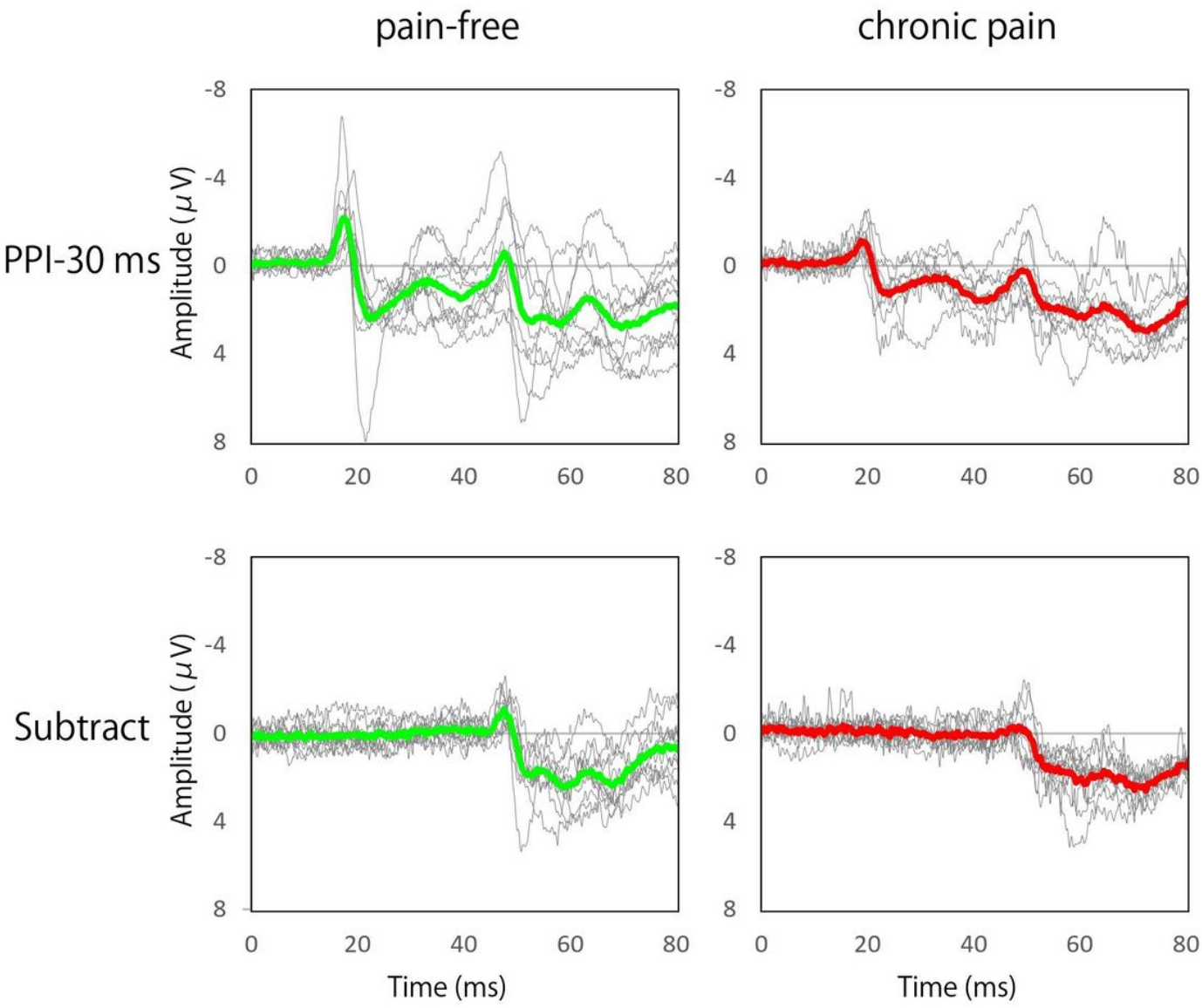

Figure 3

Grand averaged PPI_30 ms and subtracted waveforms in pain-free and chronic pain groups. Green and Red thick line show grand averaged waveforms pain-free and chronic pain athlete groups, respectively. Gray thin line shows individual waveforms.

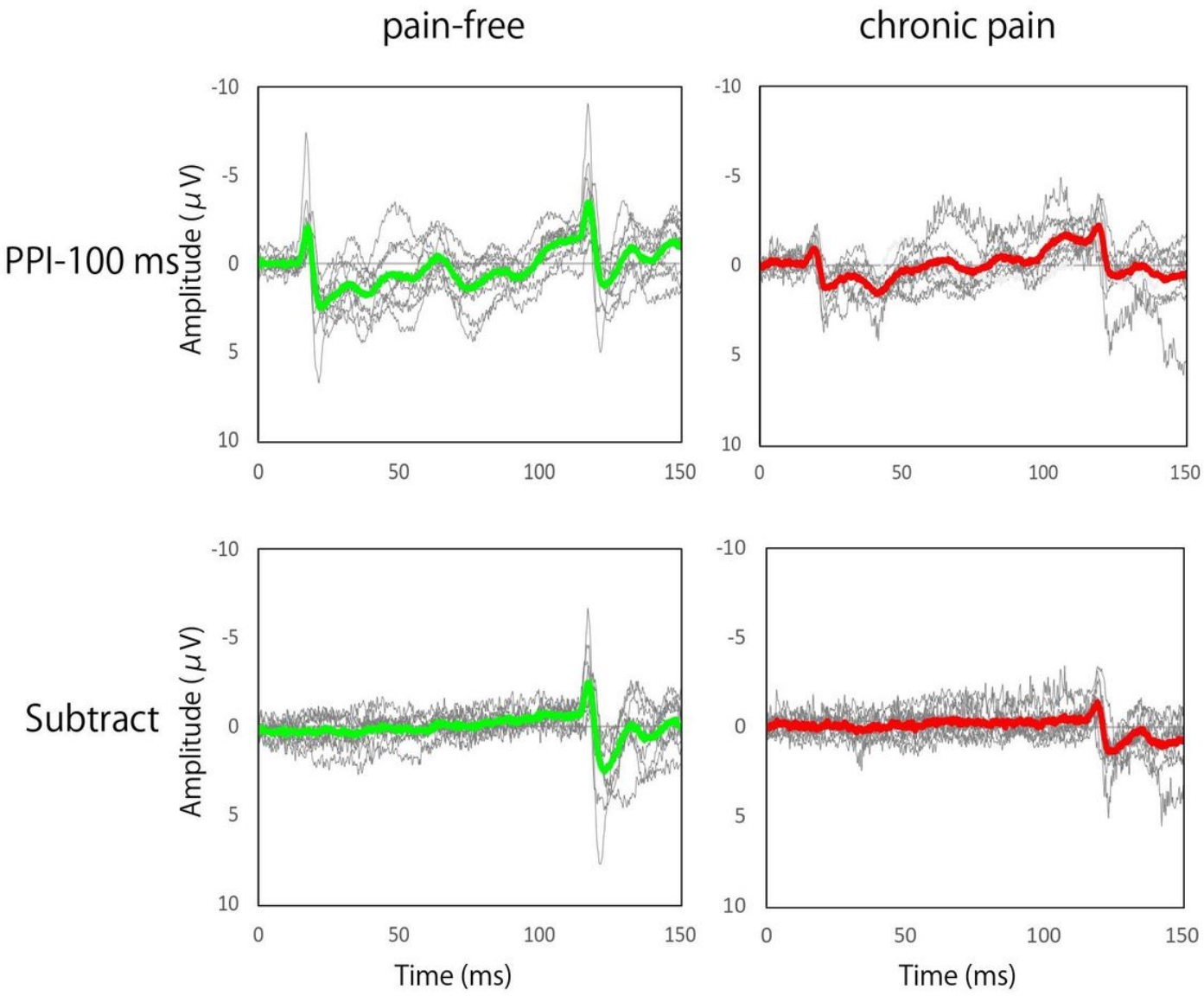

Figure 4

Grand averaged PPI_100 ms and subtracted waveforms in pain-free and chronic pain groups. Green and Red thick line show grand averaged waveforms pain-free and chronic pain athlete groups, respectively. Gray thin line shows individual waveforms.

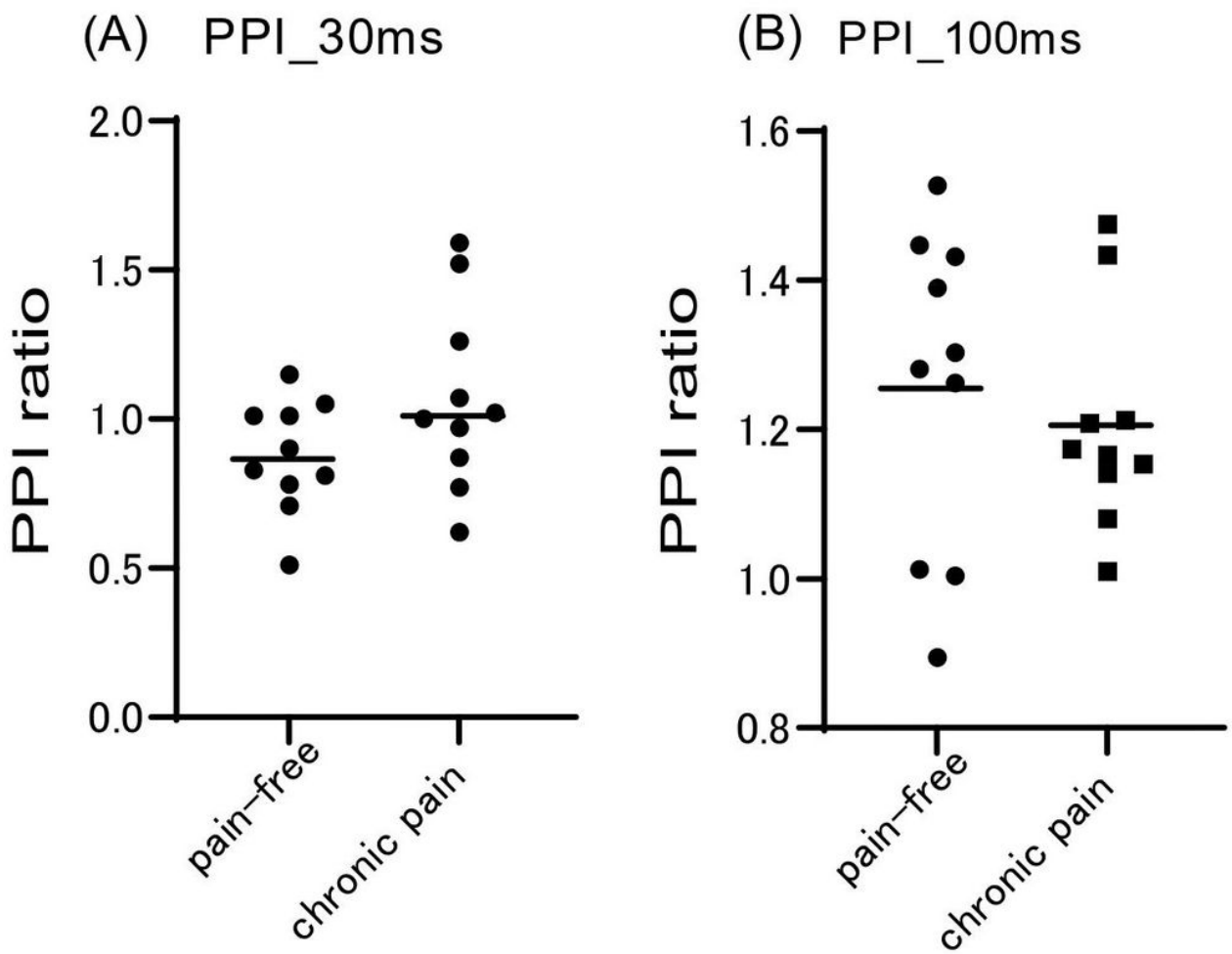

Figure 5

The PPI_30 ms and PPI_100 ms ratio are extracted for each subjects.