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Research article

Imbalance in positive and negative acceleration ratio of alpha oscillation in patients with complex regional pain syndrome

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ABSTRACT

Objectives: To elucidate the functional characteristics of the brain in the presence of chronic pain using electroencephalography (EEG), with a focus on the dynamics of neural excitation and inhibition.

Methods: Resting-state EEG was performed in: 17 patients with complex regional pain syndrome (CRPS) who exhibited chronic pain higher than 20 on the visual analogue scale (VAS), 6 patients with reduced CRPS symptoms and chronic pain less than 20 on VAS, and healthy age-matched controls. For the analysis, 50 s of electroencephalogram (EEG) signals were extracted from EEG recordings during wakefulness and rest with eyes closed. The envelope of the alpha frequency band was calculated by examining the positive and negative accelerations of the envelope oscillation, ratio of positive (Ap) to negative (An) accelerations (Ap-An ratio), and mean amplitude of the envelope. Comparisons were made between patients and controls, and correlations between these EEG measures and the subjective pain VAS were evaluated.

Significant differences in the value of Ap, An and Ap-An ratio were observed at temporal and central electrodes between patients with pain symptoms and controls. Those with reduced CRPS symptoms exhibited a distinct Ap-An ratio at the majority of electrodes when compared with those exhibiting chronic pain.

Conclusions: Distinct patterns in alpha wave envelope dynamics, reflecting excitatory and inhibitory activities, were associated with chronic pain in patients with CRPS. The pain-relieved state of CRPS suggested that a new balance of activities was established. This relationship indicated a potential association between altered alpha oscillation characteristics and the subjective experience of pain.

Significance: This study introduces a novel method for analyzing alpha oscillation envelopes, providing new insights into the neural pathophysiology of chronic pain in CRPS patients. This approach has the potential to enhance our understanding of the alterations in brain function that occur under chronic pain conditions.

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1. Introduction

Complex regional pain syndrome (CRPS) is a pain syndrome classified in the International Classification of Diseases, 11th Revision (ICD-11) as chronic post-traumatic or post-operative pain [1,2]. Recent studies indicated that the pathophysiology of CRPS involves a complex interplay of multiple systems and mechanisms, including immune dysfunction [3–5]. Moreover, patients with CRPS have been demonstrated to exhibit abnormalities in cortical activity and neural networks, as evidenced by resting electroencephalography (EEG) and magnetoencephalography (MEG) [6–8].

In recent studies, electroencephalography (EEG) has emerged as an invaluable tool for assessing brain function in relation to chronic pain. Previous reports demonstrated a correlation between EEG patterns and chronic pain [9–17]. The methods of analysis employed have varied, but in general, an increase in theta and beta band power of resting-state EEG has been suggested to be important [14,17]. However, the characteristic values of oscillation power, peak frequency, and cortical areas in patients with chronic pain were not always consistent, and the results were sometimes contradictory [9,14,17]. The functional relationship between EEG findings and brain network systems has also been investigated [8,12,13,16], but EEG characteristics in patients with chronic pain remain unclear.

Another aspect of brain dysfunction associated with chronic pain has been proposed: excitation-inhibition balance (E-I balance) [18,19]. To date, E-I balance has been reported as a phenomenon of neural activity at the molecular or synaptic level in various diseases, including dementia [20,21], schizophrenia [22,23], and developmental disorders [24]. The involvement of E-I balance in chronic pain has also been reported in animal studies [25,26] and research employing experimental methods in humans [27,28].

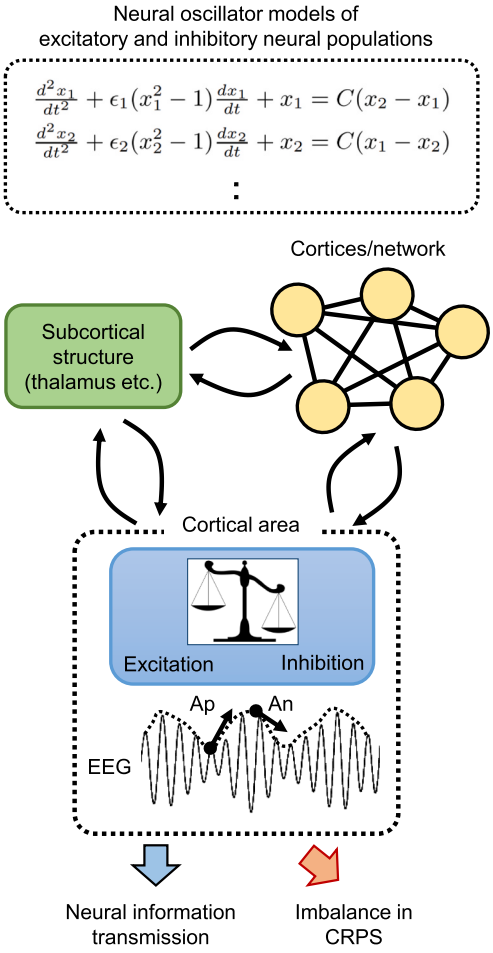

Fig. 1. Conceptual illustration of the present study. Top: Neural oscillator models, consisting of nonlinear equations of oscillation, and second-order derivatives, which can correspond to inhibitory or excitatory forces. Note: The equations are not equations for the alpha wave envelope, but simple oscillator model equations for illustrative purposes. Middle: Envelope of alpha oscillation is shaped by the interplay between excitation and inhibition within neural circuits, encompassing cortical, subcortical, and network structures. Arrows denote the positive (Ap) and negative (An) accelerations, which are the second-order time derivatives of the alpha envelope. Alpha oscillation and the envelope function to transmit information, and imbalance of excitation and inhibition may occur in brain areas of patients with complex regional pain syndrome (CRPS).

However, the correspondence of neural activity at the systems level, such as EEG, has not been well-documented. Although there are EEG analysis methods to investigate the E-I balance or related activity of the brain [29], few studies have analyzed the resting EEG in terms of the E-I balance in patients with chronic pain.

The objective of this study was to ascertain whether information on E-I balance in CRPS could be derived from EEG data. The research focused on the fluctuations in alpha wave amplitude, known as waxing and waning, which is a key component of resting-state EEG.

The envelope amplitude of the alpha wave has been thought to be formed through multiple excitatory and inhibitory processes, including modulation at the cortical, subcortical, and network levels, as well as the alpha wave amplitude itself [30–33]. The mechanisms and implications of the alpha waxing and waning and alpha oscillations itself remain unclear. However, there is a strong suggestion that these activities are related to neural information transmission [32,34,35]. Alpha oscillations have been postulated to exert an inhibitory influence on cortical activity [36–38]. However, they have also been suggested to have an excitatory function, with alpha activity acting as a modulator that shifted cortical conditions between excitation and inhibition [39]. Previous reports have hypothesized that the rhythmic nature of alpha waves mediated inhibition [36–38], while another hypothesis was that the summation of waves of multiple frequencies formed waxing and waning [40]. Both hypotheses suggested that waves or oscillations served a functional role in the transmission of information. In contrast to the aforementioned hypotheses, Lombardi et al. [39] reported that alpha waves exhibited intermittent increases or decreases in amplitude rather than a consistent rhythm [39,41,42].

In the study of mathematical models of alpha waves and their fluctuations, neural mass models (NMMs) are an important tool in mathematical modeling that explains neural activities from the level of neuronal firing to the interactions between multiple regions of the cortex [46–51]. NMMs has been also reported to be a model for explaining brain activity from the viewpoint of E-I balance, i.e., mutual control of excitatory and inhibitory neural activity [43,52].

Based on the amplitude-dependent intermittent nature of waxing and waning proposed by Lombardi et al. [39] and significance of the second-order derivative in their NNM for excitatory and inhibitory effects of alpha waves [43], we used the second-order time derivative, or acceleration, obtained from the envelope of the alpha oscillation. In this study, positive and negative second-order derivatives were calculated for the envelope of alpha oscillations. We recently analyzed accelerations of the alpha wave envelope obtained from patients with dementia using a method similar to that used in the present study [53]. The results of this analysis revealed patterns of positive and negative acceleration in the alpha wave envelope that were characteristic of types of dementia [53]. The present study employed this method to investigate whether accelerations associated with functions of excitation and inhibition, as variable components of the alpha wave oscillation, are modified by the functional pathology in CRPS.

The current study introduced a functional pathophysiology in patients with CRPS using EEG envelope analysis based on excitatory and inhibitory neural activities. One of the advantages of this method is that excitatory and inhibitory forces can be calculated for a single electrode site or single brain region. While neural connectivity and network analysis can reveal the relationship between multiple brain regions, the present method allowed us to evaluate the resulting activity in a region from the perspective of excitatory and inhibitory forces. The concept of this study and analytical method are illustrated in Fig. 1.

2. Methods

2.1. Participants

Twenty-three patients with CRPS were included in this study. The presence of CRPS was diagnosed in all patients according to CRPS criteria [54]. The participants included: 17 with pain VAS higher than 20, and 6 with pain VAS less than 20, which indicated that pain was not a central symptom of CRPS. The six participants were those who exhibited improvement in CRPS symptoms, including those who underwent re-measurement of EEG. Consequently, the six patients with low pain VAS scores were analyzed as a distinct group separate from the 17 patients with ongoing pain symptoms. Additionally, 32 healthy volunteers were included as participants in the study. Prior to its commencement, each participant was provided with detailed information regarding the nature of the study and implications of their participation. The present study was approved by the local ethics committee of the Faculty of Medicine (2015–0081, 2018–0148) at Nagoya University, in accordance with the Declaration of Helsinki [55].

2.2. Electroencephalography (EEG) measurement

EEG signals were acquired from 17 disk electrodes via an EEG system (Neurofax, EEG-1100, Nihon Kohden, Japan). The electrodes were placed according to the International 10–20 system at F3, F4, C3, C4, P3, P4, O1, O2, T1, T2, T3, T4, T5, T6, Fz, Cz, and Pz. Additionally, an electro-oculogram (EOG) was recorded from two electrodes placed 2 cm lateral to the lateral canthi and 2 cm from the lower edge of the orbit of one eye. Fp1 and Fp2 electrodes were not utilized in this study due to the frequent noise generated by eye movements and mixture of electrical noise from muscles and movements. Additionally, an electrocardiogram (ECG) was recorded in conjunction with EEG and EOG. The initial bandpass filter was between 0.1 and 100 Hz, with a sampling rate of 1000 Hz. Each participant was instructed to lie down in a quiet EEG recording room and remain awake and still for a period of more than 60 s, while their EEG was recorded with their eyes closed.

2.3. Signal analysis

ECG and EOG artifacts were initially removed from EEG signals using signal-space projection with independent component analysis

[56]. EEG signals were selected manually from a 50-s recording in a fully awake state. The signals were evaluated for saccadic EOG and dominant activity in the alpha frequency band, and they were free from extra-cephalic electrical noise such as electromyography and movement artifacts. Subsequently, a band-pass filter between 8 and 13 Hz was used to extract alpha activity at each electrode (Fig. 2-A). The baseline was then determined by averaging EEG signals over a 50-s period. A fast Fourier transform was applied to obtain the peak frequency power, which also confirmed that each participant was awake and exhibited alpha activity. These procedures were conducted using the open-source academic software Brainstorm [57], which is based on Matlab.

The following analyses, presented in Fig. 2, were conducted using MatLab commands. The envelope of the alpha waves was calculated at each electrode. The upper envelope for the alpha wave peaks was obtained using a program of MatLab commands (Fig. 2-B). The following formulae were employed to derive the envelope (f(t)) of alpha activity (g(t)):

$$h(t) = \mathrm{sqrt}\ \{\ (g(t))\hat{}2 + (H(g(t))\hat{}2\ \}$$

$$f(t) = |h(t)|$$

h(t): intermediate formula, sqrt: square root, H: Hilbert transform.

The second derivative of the envelope waveform was calculated at each sampling point (Fig. 2-C). The excitatory and inhibitory

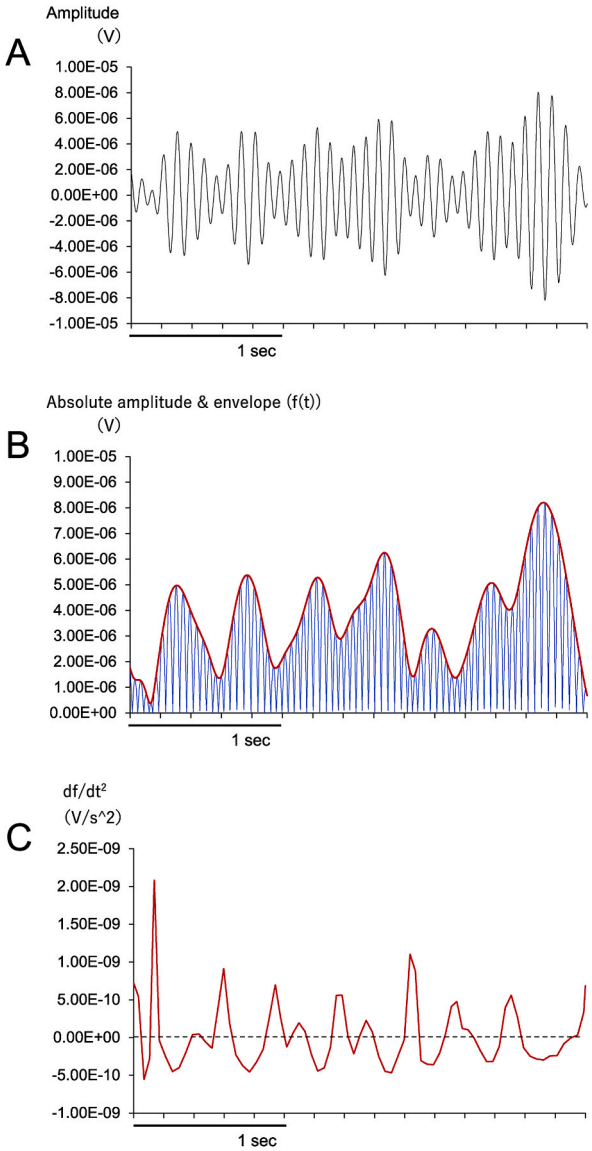

Fig. 2. Waveform analysis procedures. In this study, the resting-state EEG was processed from A to C. A: EEG signals filtered by the alpha bandpass filter between 8 and 13 Hz (black line). B: Absolute amplitude of alpha activity (blue line) and peak envelope (red line). C: Second derivative of envelope (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

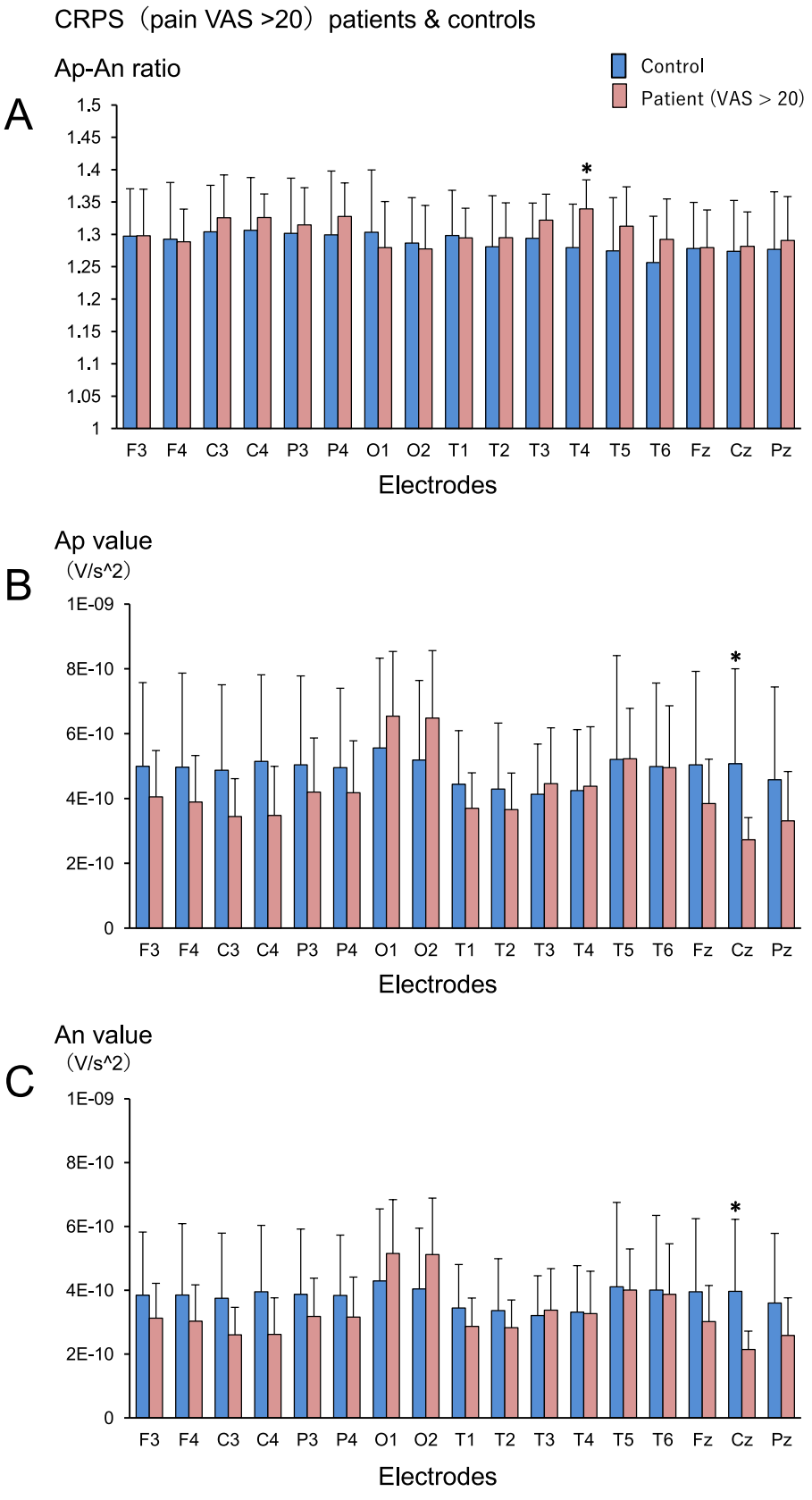

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Fig. 3. Comparisons of acceleration values between CRPS patients with pain VAS higher than 20 (red cilums) and controls (blue columns) at each electrode. A: Ap-An ratio: ratio of Ap divided by An. The Ap-An ratio at T4 was greater in patients than controls ($p = 0.0445$). B: Ap (acceleration positive) value. C: An (acceleration negative) value. Both Ap ($p < 0.0001$) and An ($p < 0.0001$) values were lower in patients than controls at Cz. *p < 0.05, FDR. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

forces that form the envelope were defined as positive and negative values of the second derivative, respectively. For a period of 50 s, the means of all positive second-derivative values exceeding zero were expressed as acceleration positive (Ap), and the means of all negative second-derivative values below zero were expressed as negative (An) values. For each electrode, the ratio of the values of Ap and An was determined and described as the Ap-An ratio. The root mean square, RMS, of amplitude of the alpha wave was obtained at each sampling point, and the value was assessed as the envelope amplitude at each electrode.

2.4. Subjective pain evaluation

The subjective pain experienced at the time of EEG measurement was quantified using a visual analogue scale (VAS), with pain perception rated on a scale from 0 (no pain) to 10 (unbearable pain).

2.5. Statistical analysis

The values of Ap, An and Ap-An ratio, and mean amplitude were compared among patient and control groups. A two-tailed *t*-test was employed to assess the significance of the values at each electrode between the groups. Subsequently, a false discovery rate (FDR, Benjamini-Hochberg procedure) was applied to account for multiple comparisons. Comparisons were made between patients and controls separately for the two groups: those in the patient group with a pain VAS higher than 20 and those in the control group, and those in the patient group with a pain VAS less than 20 and those in the control group. Furthermore, the values of Ap, An and Ap-An ratio, and mean amplitude obtained at each electrode were also compared between patient groups with pain VAS higher and less than 20.

For all 23 patients, Pearson's correlation among pain VAS and the values of Ap, An and Ap-An ratio, and mean amplitude were calculated at each electrode. Mean values for Ap, An and Ap-An ratio, and mean amplitude were also obtained for all electrodes to assess the correlation with pain VAS. A p-value less than 0.05 and *q*-value less than 0.05 obtained after the post-hoc test, FDR, were considered significant. The *q* value for FDR was determined as $p \times N/i$; N: number of multiple comparisons, *i*: *p*-value rank. Evaluation by the correlation coefficient was statistically provisional because the data included patients with pain VAS of less than 20 who underwent re-measurement after recovery from CRPS symptoms.

3. Results

3.1. Participants and data acquisition

EEG signals were successfully obtained from both patients and controls. The main group of CRPS patients was comprised of 17 patients with pain VAS of 20 or higher. Six patients with pain VAS of less than 20 were treated as a separate group and had their EEG re-measured after improvement in subjective pain symptoms of CRPS. The interval between the initial and second measurements was at least three but less than six months.

Table 1
Profiles of participants.

	CRPS patients (Pain VAS > 20)	Control-1	CRPS patients (Pain VAS <20)	Control-2
n	17	25	6	20
Mean age (years)	54.82	54.12	38.33	37.95
(SD)	(13.75)	(15.66)	(16.16)	(12.17)
Age range	33–86	32–83	18–53	20–55
F: M	10 : 7	16 : 9	4 : 3	13 7
Mean pain VAS	64.18	–	12.83	–
	(21.12)		(4.84)	
Pain VAS range	27–97	–	7–18	–
*Mean peak frequency (Hz)	9.94	9.76	10.00	10.10
(SD)	(0.89)	(0.88)	(0.63)	(0.91)
Frequency range	9–11	9–11	9–11	9–11

*CRPS: complex regional pain syndrome.
*VAS: visual analogue scale.
*Mean peak frequency for all electrodes.
*Control-1: control participants for CRPS patients with pain VAS higher than 20.
*Control-2: control participants for CRPS patients with pain VAS less than 20.

The profiles of participants in the patient and control groups are presented in Table 1. There were no significant differences in the age, sex ratio, or frequency with the highest power in the alpha frequency band averaged over all electrodes between patient and control groups (Table 1).

3.2. Pain VAS

Seventeen patients exhibited pain VAS higher than 20 at the time of the experiment (n = 17, F:M = 10:7, mean age: 54.8 ± 13.7 (SD)). Six patients exhibited VAS less than 20 (n = 6, F:M = 4:2, 38.3 ± 16.2). The six patients were evaluated as a subgroup. Given the disparate age distributions observed between pain VAS subgroups, subgroups with pain VAS less or higher than 20 were compared with age-matched control subgroups (n = 20, F:M = 13:7, 39.0 ± 9.8; n = 25, F:M = 16:9, 54.1 ± 15.7, respectively). There were no significant differences in age, sex ratio, or the frequency with the highest power in the alpha frequency band averaged over all electrodes between the patient and control groups (Table 1).

3.3. Ap-An ratio, Ap and An values, and envelope amplitude

The mean values and standard deviations (SD) of the values of Ap, An and Ap-An ratio, and envelope amplitude obtained at each electrode in the patient and control groups are presented in Supplementary Data (S-Table 1).

3.3.1. Patients with CRPS and pain VAS higher than 20 (Fig. 3 (A-C) and 5 (A), S-Table 2)

Statistical results of all comparisons are presented in Supplementary Data (S-Table 2). The mean Ap-An ratio was larger in the patient than control groups ($t(16) = 2.821$, $p = 0.0110$, *t*-test) for all 17 electrodes. Multiple comparisons among 17 electrodes showed that the Ap-An ratio at T4 was significantly greater in patients than controls ($q = 0.0445$, corrected by FDR) (S-Table 2-1) (Fig. 3 (A)). Ap ($t(16) = -2.612$, $p = 0.0189$, *t*-test) and An ($t(16) = -2.754$, $p = 0.0139$, *t*-test) values were both smaller in the patient than control groups for all electrodes. A series of statistical tests revealed that Ap ($q = 0.0428$) and An values ($q = 0.0397$) at Cz were significantly lower in the patient than control group (Fig. 3 (B and C), S-Tables 2-2 and 2-3). The mean amplitude of the envelope was found to be smaller in the patient than control group for all electrodes ($t(16) = -7.370$, $p < 0.0001$, *t*-test). The results of multiple comparisons indicated that values at Cz ($q = 0.0357$, corrected by FDR), C3 ($q = 0.0329$), and Pz ($q = 0.0299$) were significantly smaller in the patient than control group (S-Table 2-4).

3.3.2. Patients with CRPS and pain VAS less than 20 (Fig. 4 (A-C) and 5 (B), S-Table 3)

The statistical results of all comparisons are presented in Supplementary Data (S-Table 3). The mean Ap-An ratio was found to be smaller in the patient than control group ($t(16) = -10.421$, $p < 0.0001$, *t*-test) for all electrodes. For each electrode, multiple comparisons revealed that the value was lower at O2 ($q = 0.0217$, corrected by FDR), T1 ($q = 0.0384$), O1 ($q = 0.0321$), F3 ($q = 0.0254$), T6 ($q = 0.00888$), Fz ($q = 0.0325$), P3 ($q = 0.0319$), P4 ($q = 0.0355$), and Cz ($q = 0.00339$) (Fig. 4 (A)).

The Ap value ($t(16) = -10.330$, $p < 0.0001$, *t*-test) was smaller in both the patient and control groups (Fig. 4 (B)). Similarly, the An value ($t(16) = -8.496$, $p < 0.0001$) was also smaller in the patient than control group. No significant differences were observed for any electrode following multiple comparisons (*t*-test, FDR) (Fig. 4 (C)).

The envelope amplitude did not differ between the patient and control groups ($t(16) = -0.806$, $p = 0.432$, *t*-test), and no difference in value was observed at any electrode following multiple comparisons (*t*-test, FDR) (Fig. 5 (B)).

3.4. Comparison between patients with pain VAS higher and less than 20 (S-Table 4)

Statistical results of all comparisons are presented in Supplementary Data (S-Table 4). The mean Ap-An ratio was greater in patients with pain VAS higher than 20 than in those with pain VAS less than 20 ($t(16) = 15.218$, $p < 0.0001$, *t*-test) for all 17 electrodes. The Ap value was greater in patients with pain VAS higher than 20 than in those with pain VAS less than 20 ($t(16) = 8.014$, $p < 0.0001$), and the An value was greater in patients with pain VAS higher than 20 than in those with pain VAS less than 20 ($t(16) = 5.547$, $p < 0.0001$, *t*-test). The envelope amplitude was lower in patients with pain VAS higher than 20 than in those with pain VAS less than 20 ($t(16) = -6.673$, $p < 0.0001$, *t*-test).

At electrodes except T2 and Pz, the value of Ap-An ratio was significantly greater in patients with pain VAS higher than 20 than in those with pain VAS less than 20 ($p < 0.05$, FDR) (S-Table 4-1).

There was no difference in Ap and An values or envelope amplitude at any electrode after multiple comparisons between patient subgroups (S-Tables 4-2, 4-3, 4-4).

3.5. Correlations among pain VAS and the values of Ap, An and Ap-An ratio, and envelope amplitude in patients with CRPS

The correlations among pain VAS and the values of Ap, An and Ap-An ratio, and envelope amplitude were assessed using data obtained from patients with pain VAS higher/less than 20. Correlation coefficient scores were statistically provisional because they included data from patients with pain VAS of 20 or less who were re-assessed after recovery from CRPS symptoms. Statistical results of all correlations at electrodes are presented in Supplementary Data (S-Table 5). The correlation between the mean Ap-An ratio obtained from all electrodes in each patient and pain VAS was significant (n = 23, r = 0.585, p = 0.00336) (Fig. 6 (A)). Pain VAS did not correlate with mean Ap and An values or envelope amplitude for all electrodes (Fig. 6 (B-C)). Significant positive correlations between

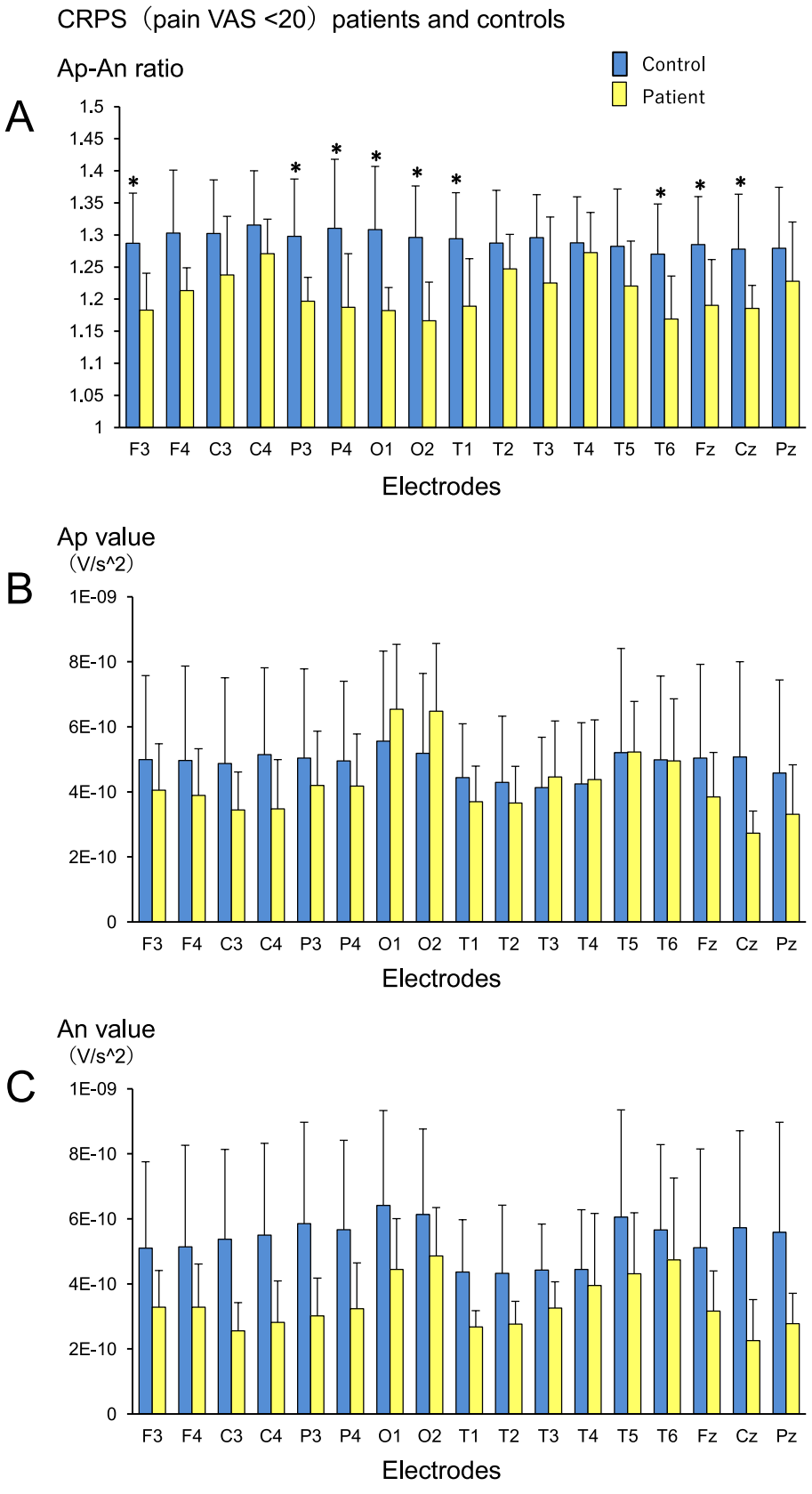

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Fig. 4. Comparisons of acceleration values between CRPS patients with pain VAS less than 20 (yellow columns) and controls (blue columns) at each electrode: A: Ap-An ratio: ratio of Ap divided by An. The Ap-An ratio was lower at O2 ($p = 0.0486$), T1 (0.0384), O1 (0.0321), F3 (0.0254), T6 (0.0302), Fz (0.0325), P3 (0.0319), P4 (0.0355), and Cz (0.0338). B: Ap (acceleration positive) value. C: An (acceleration negative) value. There was no significant difference in Ap and An values for each electrode. *$p < 0.05$, FDR. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

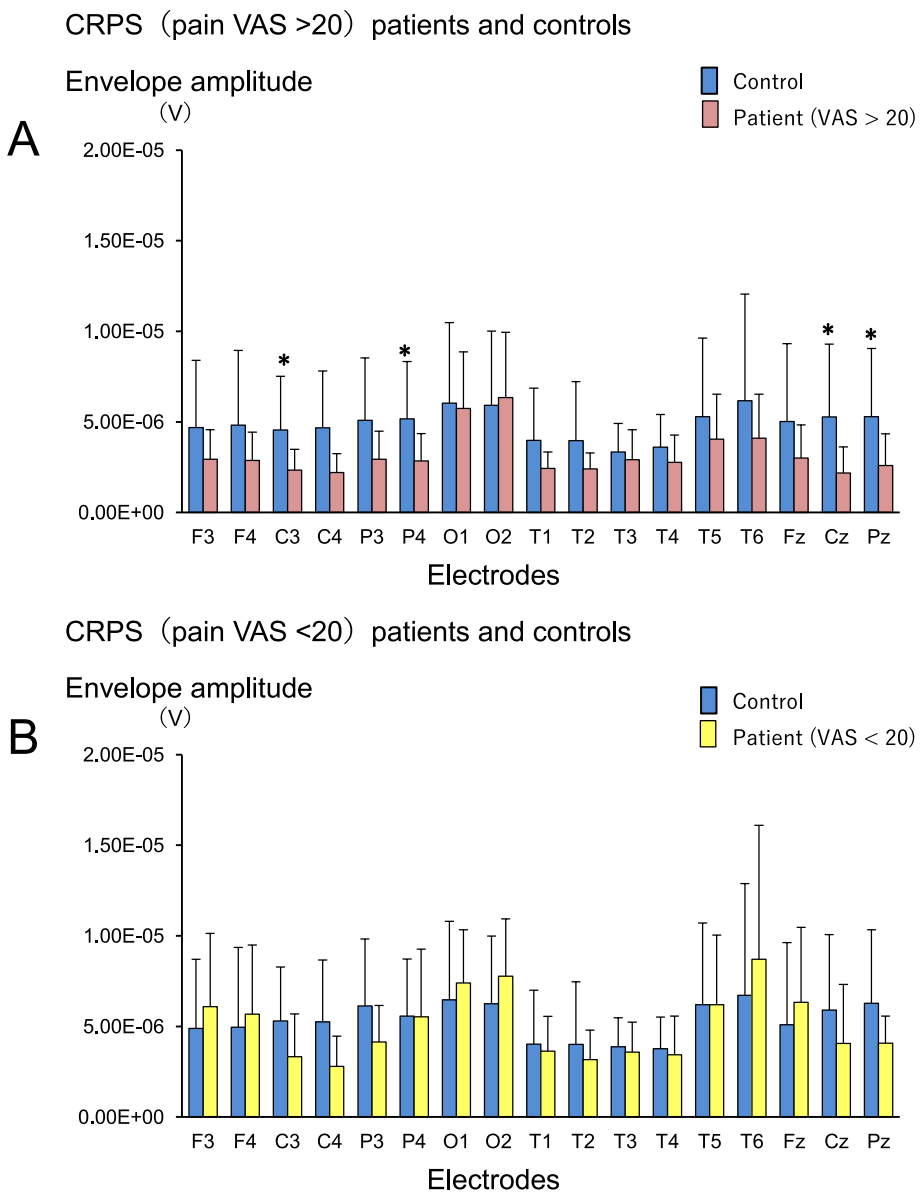

Fig. 5. Comparisons of mean envelope amplitude between patients and controls. A: Comparisons of mean envelope amplitude between patients with pain VAS higher than 20 (red columns) and controls (blue columns). Multiple comparisons showed that the values at C3 ($p = 0.0330$), Cz (0.0357), P4 (0.0329), and Pz (0.0299) were smaller in the patients than controls ($p < 0.05$, FDR). B: The mean envelope amplitude differed between patients with pain VAS less than 20 (yellow columns) and controls (blue columns). No difference was found at any electrode. *$p < 0.05$, FDR. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Ap-An and pain VAS were noted at P3 ($r = 0.634$), T6 (0.622), T1 (0.612), P4 (0.610), T3 (0.566), and Cz (0.563) after multiple comparisons (Fig. 7, S-Table 5-1). The Ap and An values and envelope amplitude did not show any significant correlation with pain VAS (S-Tables 5-2, 5-3, 5-4).

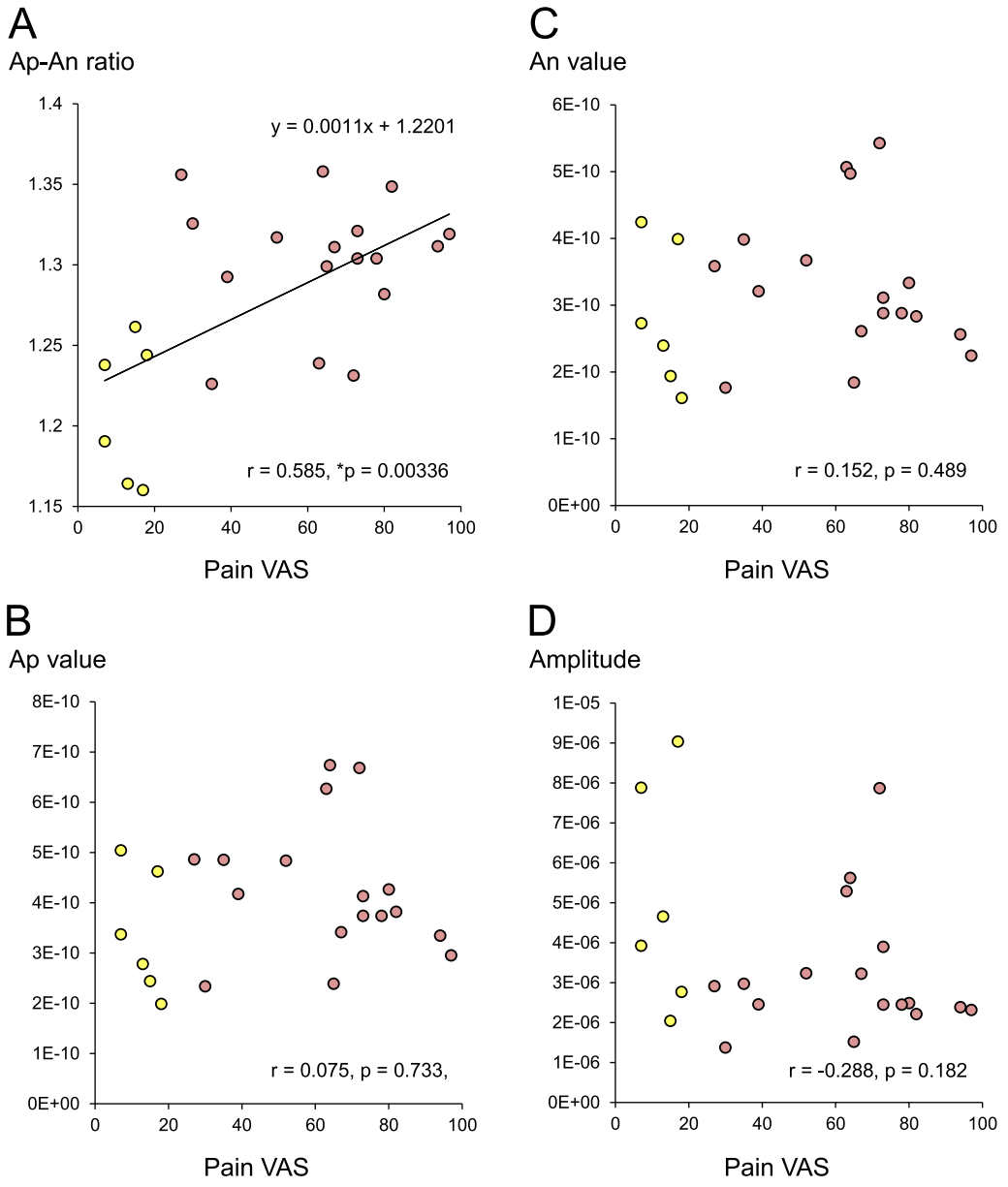

Fig. 6. Correlation between mean acceleration values and the pain VAS for all electrodes. A: Ap-An ratio: ratio of Ap divided by An. B: Ap (acceleration positive) value. C: An (acceleration negative) value. D: Amplitude of the envelope of alpha waves. Red circles indicate patient participants with pain VAS higher than 20 (n = 17). Yellow circles indicate patient participants with pain VAS less than 20 (n = 6), and their EEG was re-measured after improvement in subjective pain symptoms of CRPS. The correlation between the mean Ap-An ratio for all electrodes in the patients (n = 23) and pain VAS was significant. A correlation curve is shown for the correlation between the Ap-An ratio and pain VAS. Pain VAS did not correlate with mean Ap and An values or the envelope amplitude for all electrodes. r; Pearson's correlation coefficient, *p < 0.05.

4. Discussion

The main results of the present study can be summarized as follows: 1) parameters related to the alpha wave envelope, the values of Ap, An and Ap-An ratio, and envelope amplitude, could be applied to assess differences in neural activity between patients with CRPS and control groups; 2) there was a significant correlation between the Ap-An ratio and subjective pain VAS in patients with CRPS; 3) parameters might not return to normal patterns in patients whose CRPS symptoms have subsided. The envelope of alpha waves in clinical EEG has received little attention as an indicator of brain function and dysfunction, but the results of this study suggest that the envelope of alpha waves might be a biological indicator of functional neural regulation, including excitatory and inhibitory neural activities.

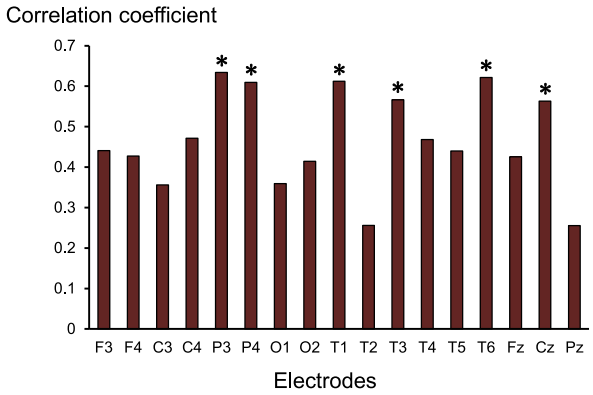

Fig. 7. The correlation between the Ap-An ratio and pain VAS at each electrode for all patients with CRPS. Significant positive correlations were noted between the Ap-An ratio and pain VAS at multiple electrodes, including P3 (r = 0.634, p = 0.0197, FDR), T6 (0.622, 0.0131), T1 (0.612, 0.0108), P4 (0.610, 0.0086), T3 (0.566, 0.0164), and Cz (0.563, 0.0146), after multiple comparisons.

4.1. Analysis of the alpha wave envelope; a biomarker of excitatory and inhibitory neural activities

Alpha activity is a dominant activity of EEG in terms of frequency power and has been reported as a consistent indicator of pathophysiology in patients with chronic pain [11,58,59]. Previous studies used alpha wave frequency analysis [58,59] and power measurement [11] as indicators of chronic pain. It has been reported that frequencies other than alpha waves, theta, beta, and gamma rhythms, in EEG were used as indicators of chronic pain [9,10,12,15,16]. These studies involved analyses based on EEG rhythms. The novel perspective applied in this study was not the alpha wave or its frequency itself, but the forces acting on the amplitude fluctuation of the alpha wave, i.e., the calculated envelope. Based on the proposed neural model, the transmission of information on neural excitation and inhibition is based not only on the rhythm of the wave, but also on the amplitude, force, and second-order differential components of the wave at any given time [39,41–43]. It was suggested that the alpha oscillations had inhibitory [36–38] and excitatory effects on the cortex, acting as a modulator that shifted cortical conditions between excitation and inhibition [39]. Therefore, the novel method of the present analysis involved calculating the ratio of forces applied to the alpha wave fluctuations, which we considered to be the observation of a factor related to the regulation of excitation and inhibition during rest. However, since the function of alpha waves involves inhibition in the cortex, as described above, neither the Ap-An ratio nor Ap and An are directly related to the excitation and inhibition of neural activity, even if they are forces that increase or decrease the alpha wave envelope.

The EEG alpha rhythm was considered to be generated primarily in the thalamus [44], but it has been reported that the rhythm was generated not only in the thalamus but, at least in part, in each area of the cortex [32,45,60]. If this is the case, the behavior of alpha waves in each cortical region may vary individually with the function of that region and its role in the neural network. Alpha oscillations have not only a frequency and amplitude, but also an envelope whose amplitude fluctuates within a certain range. The envelope of a frequency has been widely used for connectivity analysis, such as amplitude-envelope correlation analysis [61–65]. However, analysis of the alpha wave envelope itself was limited in previous studies [32,66–69].

We hypothesized that this envelope and its excitatory and inhibitory effects fluctuated uniquely in each cortical region as a function of each neural network, depending on the function and pathology in the patient. In our recent study, the values of Ap-An ratio were altered at EEG electrodes corresponding to the regions degenerated in dementia of Alzheimer's type and frontotemporal lobar degeneration [53]. In some types of dementia with brain atrophy, loss of neural cells might affect the Ap-An ratio [53]. In this study, we tested whether the same analytical method could be used for functional pathology in patients with CRPS. The Ap-An ratio used in this study has the advantage that it can be calculated for alpha activity derived from a single electrode. If analysis with current source estimation is available for a brain region, this value, the Ap-An ratio, can be calculated for individual brain regions. When the region is a hub or lesion in the network, it may be possible to infer function/dysfunction in the neural network by knowing the state of excitation and inhibition in that region, although further research is needed.

4.2. Difference in the envelope parameters between patients with CRPS and controls

The values of Ap, An and Ap-An ratio, and envelope amplitude, differed among patients with CRPS. Electrodes showing differences between groups were vertex (Cz for the Ap and An values) and temporal (T4 for the Ap-An ratio) electrodes. A previous study reported that there was hypersensitivity of the brain network in patients with chronic pain at rest [6]. The Ap-An ratio was significantly larger in the patient than in control group, and the envelope amplitude was smaller in the patient than in control group at electrodes C3, P3, Cz, and Pz. A decrease in alpha activity, which has an inhibitory function [36–38], could cause disinhibition, but interpretation might not be straightforward because the decreased alpha activity in terms of the amount did not necessarily suggest a functional decrease, but the changes the Ap-An ratio could be due to a compensatory suppression. The envelope amplitude and Ap-An ratio could interact, and regardless of this, the excitation-inhibition balance and the resulting envelope amplitude were considered to be altered in the patient group.

With regard to brain areas, the cingulate cortex, secondary sensory cortex (SII), insula, and precuneus, all reportedly important hubs in pain-related networks [70], were reported as possible cortical areas responsible for chronic pain in CRPS in previous reports [7, 71–73]. The pain-related brain areas involved midline and bilateral structures, such as the cingulate, insula, and SII cortices, and electrodes corresponding to these areas could be midline and temporal electrodes, where there were differences in the Ap-An ratio and envelope amplitude between patients with CRPS and controls. However, it is difficult to discuss brain regions based on the results obtained from 17 electrodes of conventional clinical EEG recording.

4.3. Correlation of the Ap-An ratio with subjective pain VAS

The value of Ap-An ratio was correlated with subjective pain, although the results were provisional because multiple measurements were included in the analysis due to the small number of patients. Electrodes showing significant correlations were parietal, temporal, and Cz electrodes. As mentioned above, it is difficult to identify brain regions from 17 electrodes, but the Ap-An ratio was shown to correlate with the degree of subjective pain more than with the EEG amplitude. In the patient groups, the Ap-An ratio increased as subjective pain increased. Since neither Ap nor An correlated with subjective pain, it was not possible to determine whether this was due to increased positive or decreased negative acceleration. In addition, although chronic pain was a major symptom of patients with CRPS, it should be noted that the present study could not distinguish whether brain activity was caused solely by chronic pain or another pathophysiology of CRPS, such as motor disability.

4.4. The Ap-An ratio in patients with mild subjective pain

Six patients who recovered from the severe stage of CRPS and reported a pain VAS of 20 or less at the time of the experiment differed from the controls regarding the Ap-An ratio, but not envelope amplitude. In patients with pain VAS less than 20, the Ap-An ratio was lower than controls. Because of the small number of patients with pain VAS of 20 or less, the present results should be investigated with a larger number of patients. However, CRPS patients whose pain was reduced by treatment and their progress suggested that, at least up to 6 months after pain reduction, brain activity might not have returned to normal but may have reached a new balance.

5. Limitations

A problem affecting many studies on CRPS is the small number of subjects because it is a rare condition. In addition, patients' subjective complaints of chronic pain were sometimes unreliable, so care must be taken in selecting patients. The numbers of subjects in subgroups was also small and age-biased in the present study. Further studies with a larger number of patients are needed. At the same time, because CRPS symptoms fluctuated within individuals during the disease course, it was also important to repeatedly evaluate when symptoms change within the same patient, as was the case with some of the patients included in this study. The present study was conducted using 17 electrodes of conventional EEG recording with the International 10–20 system. We consider that it was possible to show the characteristics of the envelope even with the small number of electrodes, but a high-density EEG or MEG system should be applied for whole-brain analysis to identify brain regions responsible for chronic pain-related Ap-An ratio changes. The current study compared the association with subjective chronic pain, but it was unclear whether the results were due to chronic pain that is common to other chronic pain disorders, or specific to CRPS alone.

6. Conclusion

In the present study, the envelope of alpha activity in terms of excitatory and inhibitory activities was different in patients with chronic pain, which was related to subjective pain. We applied a novel analysis method to the envelope of alpha oscillation, which may be a novel component of cortical neural activity in addition to the frequency and amplitude. Significance: The Ap-An ratio, calculated from the second derivative of the alpha wave envelope, may be a useful biomarker for each brain site for functional neural modulation caused by chronic pain, which has not been proposed before.

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Ethical declaration

The present study was approved by the local ethics committee of the Faculty of Medicine (2015–0081, 2018–0148), Nagoya University, on the basis of the Declaration of Helsinki.

Data availability

The data used in this study have not been deposited in a publicly accessible repository, as the authors do not have permission to share clinical data.

CRediT authorship contribution statement

Misako Sano: Writing – original draft. **Katsuyuki Iwatsuki:** Writing – review & editing, Data curation, Conceptualization. **Hitoshi Hirata:** Writing – review & editing, Funding acquisition, Conceptualization. **Minoru Hoshiyama:** Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that may appear to have influenced the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36463.

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