



Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex



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HIGHLIGHTS

- Low dose of perampanel (PER) is tolerable and effective to ameliorate refractory cortical myoclonus.
- PER suppresses and disperses paroxysmal depolarization shifts directly on the postsynaptic neurons.
- This action was reflected by temporal dispersion in giant SEPs (a potential clinical biomarker).

ABSTRACT

Objective: To elucidate the effects of perampanel (PER) on refractory cortical myoclonus for dose, etiology and somatosensory-evoked potential (SEP) findings.

Methods: We examined 18 epilepsy patients with seizure and cortical myoclonus. Based on data accumulated before and after PER treatment, correlations among clinical scores in myoclonus and activities of daily life (ADL); early cortical components of SEP; and PER blood concentration, were analyzed.

Results: PER (mean dose: 3.2 ± 2.1 mg/day) significantly improved seizures, myoclonus and ADL and significantly decreased the amplitude of and prolonged latency of giant SEP components. The degree of P25 and N33 prolongations (23.8 ± 1.6 to 24.7 ± 1.7 ms and 32.1 ± 4.0 to 33.7 ± 3.4 ms) were significantly correlated with improved ADL score (p = 0.019 and p = 0.025) and blood PER concentration (p = 0.011 and p = 0.025), respectively.

Conclusions: Low-dose PER markedly improved myoclonus and ADL in patients with refractory cortical myoclonus. Our results suggest that SEP, particularly P25 latency, can be used as a potential biomarker for assessing the objective effects of PER on intractable cortical myoclonus.

Significance: In this study, PER lessened the degree of synchronized discharges in the postsynaptic neurons in the primary motor cortex.

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1. Introduction

Progressive myoclonus epilepsy (PME) is an epilepsy syndrome characterized by epileptic seizures and other progressive neurological symptoms such as cortical myoclonus, cerebellar ataxia, and cognitive impairment (Marseille Consensus Group, 1990; Avanzini et al., 2016). The cortical myoclonus in PME is generally progressive and medically intractable, leading to poor outcomes and affecting activities of daily life (ADL) (Shahwan et al., 2005). Although some antiepileptic and antimyoclonic drugs are effective for cortical myoclonus, their effectiveness is limited according to the type or stage of disease (Minassian, 2002; Magaudda et al., 2004).

Perampanel (PER) is a selective noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that was recently introduced as an adjunctive therapy for patients with epilepsy (Trinka et al., 2016; Krauss et al., 2013). Recent studies reported that a relatively low dose of PER reduced not only the frequency of epileptic seizures but also drastically ameliorated cortical myoclonus, subsequently improving ADL in a small subset of patients with cortical myoclonus (Unverricht-Lundborg disease [ULD] and Lafora disease) (Schorlemmer et al., 2013; Goldsmith and Minassian, 2016; Crespel et al., 2017). However, those were still very limited experiences with regard to the number of patients, and the mechanisms underlying the clinical effects of low-dose PER on cortical myoclonus remain unclear.

Several recent studies have highlighted the pharmacological characteristics of PER, such as (1) dose-dependent reduction of seizure and myoclonus (Trinka et al., 2016); (2) possible threshold dosage, e.g., 6 mg/day (maximum dose of PER is generally 12 mg/day) for severe side effects (Crespel et al., 2017); and (3) very slow titration was recommended to avoid side effects (Hanada et al., 2011; Crespel et al., 2017). These studies have suggested that the optimal dose of PER may vary among both diseases and patients. These key findings should be further investigated with respect to physiological features of cortical myoclonus.

To explore the mechanisms of PER on myoclonus, it is critical to investigate the effect of PER on cortical brain activity. In electrophysiological examinations of patients with cortical myoclonus, giant somatosensory-evoked potentials (SEPs), abnormally enhanced long-latency reflexes (C-reflexes), and a preceding spike in jerk-locked back averaging are known to reflect the degree of cortical hyperexcitability of the primary sensorimotor cortex (S1-M1) (Shibasaki, 1988; Ikeda et al., 1995; Shibasaki and Thompson, 2011). Furthermore, long-term observational studies have suggested that the SEP amplitude of P25 and N35 (N33) represents the clinical course well in patients with cortical myoclonus from benign adult familial myoclonus epilepsy (BAFME) and may be a surrogate marker of cortical hyperexcitability in patients with ULD (Hitomi et al., 2011; Kobayashi et al., 2014). In this regard, several anti-epileptic drugs (AEDs) tend to reduce SEP amplitude (Rothwell et al., 1984; Erdem et al., 2001; Striano et al., 2005). In contrast, changes in SEP latencies in accordance with AED treatment are reportedly none or highly limited (Canafoglia et al., 2004). Based on the SEP findings in cortical myoclonus, we hypothesized that the amplitude and latency of particular SEP components that reflect cortical excitability may correlate with PER treatment response in cortical myoclonus.

By taking all these concerns into account, this study aimed to evaluate the clinico- and pharmaco-electrophysiological effects of PER on cortical myoclonus to elucidate the mechanisms of action of PER and the ideal PER dosage with regards to effectiveness and side effects.

2. Methods

2.1. Patient population

In this retrospective case accumulation study, we reviewed patients suffering from refractory cortical myoclonus in Kyoto University Hospital and Takeda General Hospital from 2016 to 2017. This study was approved by the ethics committee of Kyoto University Graduate School of Medicine (IRB #R0483/1625). Inclusion criteria included patients (1) with seizures and cortical myoclonus due to PME (ULD, BAFME, dentatorubral-pallidoluysian atrophy [DRPLA], or Gaucher disease) or Lance-Adams syndrome (LAS), and (2) administrated with PER to treat seizures and cortical myoclonus during the study period. Included were 18 patients (10 males and eight females) with a mean age of 48.4 ± 16.2 years (range: 22–71 years) in this study (Table 1). Mean age at disease onset was 23.7 ± 11.5 years (range: 9–50 years). Duration of disorders varied from 3 to 53 years (24.7 ± 15.5 years). This population was comprised from ULD ($n = 7$), BAFME ($n = 6$), DRPLA ($n = 2$), Gaucher disease ($n = 1$), and LAS ($n = 2$) patients. The diagnosis of the diseases was performed based on clinical symptoms and course, neurophysiological examinations, neuroimaging, family history, and genetic studies in some patients. All of the patients with DRPLA and Gaucher disease, and some patients with BAFME (5/6) and ULD (4/7) were diagnosed through genetic testing. Patient 11 was clinically diagnosed as “definite BAFME” (without genetic examination) according to the diagnostic criteria (Kobayashi et al., 2018). Three patients (Patient 5, 6, and 7) were clinically diagnosed with “probable ULD” (without genetic examination) as they had generalized tonic clonic seizures, progressive myoclonus, ataxia, and EEG abnormality (photosensitivity and/or generalized spikes) (Kälviäinen et al., 2008). Due to its prevalent morbidity, and the medically refractory nature of chronic posthypoxic myoclonus and cortical myoclonus, LAS was also included in this study. Although a limited number of cases have been reported (Santamarina et al., 2015; Steinhoff et al., 2016), comprehensive research on the effects of PER for LAS patients has yet to be performed. Clinico-electrophysiological effects of PER on LAS are of interest; since patients with LAS may manifest not only reticular reflex myoclonus but also cortical myoclonus when the main features are action myoclonus or they have epileptic discharges in EEGs (Brown et al., 1991; Caviness and Brown, 2004) as shown in our patients.

All patients received AED therapy before PER administration, and most of them received two or more AEDs including valproate or clonazepam.

2.2. Clinical course and study design

All patients visited our clinics every 1–3 months and underwent regular clinical work up including PER treatment for seizures and cortical myoclonus. Status of seizures and myoclonus were assessed at every visit. After commencing PER treatment at an initial dosage range of 0.5–2.0 mg/day, the dose of PER was increased gradually after every 30 days (or more) up to the optimal dose by both treatment responsiveness and side effects. The daily dosage was increased by 0.5 mg/day in 10 patients, while it was increased by 1.0 or 2.0 mg/day in the remaining eight patients. The mean dosage reached 3.2 ± 2.1 mg/day (median dosage: 2.6 mg/day) with a mean follow-up period of 36.6 ± 68.9 weeks. Depending on their clinical needs, SEPs were evaluated in most patients before PER administration and were also evaluated at 2 to 6 months following the initial administration.

In this study, we retrospectively collected clinical data for each patient. The changes in clinical parameters, SEP findings, and C

Table 1
Patient characteristics, clinical, and neurophysiological findings.

Pt No.	Disease (Age, Sex)	Myoclonus		ADL		Giant SEP***			Temporal dispersion (P25/N33)	C-reflex		PER		Concomitant drugs
		Score		Score		Before	After			Before	After	(mg)	(ng/mL)	
		Before	After	Before	After		Decrement (P25/N33)	Prolongation (N20/P25/N33)						
1	ULD (34, F)	3	1	21	12	+	+/+	+/+/+	+/+	+	–	4.0	690	VPA, LEV, CZP, PIR
2	ULD (32, F)	4	3	25	18	+	+/+	+/+/+	+/+	+	N/A	2.25	366	VPA, TPM, CZP, PIR, BZD
3	ULD (67, M)	3	2	18	15	–	N/A	N/A	N/A	+	N/A	4.0	112	VPA, CZP, PB, PIR
4	ULD (57, M)	4	2	23	19	+	+/+	–/+/+	+/+	N/A	+	2.0	78	LEV, VPA, PB, CZP, ZNS, BZD
5	ULD (28, F)	3	2	18	10	+	+/+	+/+/+	+/+	+	–	3.0	214	CZP, PIR, BZD
6	ULD (70, M)	3	2	N/A	N/A	–	N/A	N/A	N/A	–	N/A	3.0	N/A	VPA, CZP, PB, TPM, PIR
7	ULD (22, F)	3	1	10	10	–	N/A	N/A	N/A	–	N/A	2.0	242	VPA, CZP
8	BAFME (49, M)	2	N/A	1	N/A	+	N/A	N/A	N/A	–	N/A	0.5	192	VPA
9	BAFME (46, F)	2	2	5	2	+	+/-	+/-/-	-/-	+	+	1.0	154	VPA, CZP, BZD
10	BAFME (65, M)	2	2	3	2	+	+/+	-/-/+	-/+	+	+	1.5	86	VPA, CZP
11	BAFME (65, F)	3	2	13	9	+	+/+	+/-/+	-/+	N/A	N/A	2.25	110	LEV, CZP, PIR
12	BAFME (71, F)	3	3	4	2	+	+/+	+/+/+	+/+	+	–	1.0	197	VPA, CZP, PIR
13	BAFME (67, F)	1	0	3	0	+	(+/+)	(+/+/+)	N/A	N/A	N/A	3.0	192	VPA, CZP, BZD
14	DRPLA (40, M)	3	2	20	18	N/A	N/A	N/A	N/A	N/A	N/A	2.0	28	VPA, CZP, LEV, ZNS, BZD
15	DRPLA (46, M)	3	1	20	19	–	N/A	N/A	N/A	–	N/A	4.0	466	VPA, LEV
16	LAS (47, M)	4	3	21	15	N/A	N/A	N/A	N/A	N/A	N/A	10.0	N/A	LEV, CZP, PRM, CBZ, BZD, PIR
17	LAS (31, M)	2	2	11	8	N/A	N/A	N/A	N/A	N/A	N/A	4.0	279	CZP, PIR
18	GD (34, M)	2	1	5	4	+	+/+	+/+/+	+/+	N/A	–	3.5	344	VPA, LEV

Abbreviations: ADL, activities of daily life; BAFME, benign adult familial myoclonus epilepsy; BZD, benzodiazepine; CBZ, carbamazepine; CZP, clonazepam; DRPLA, dentatorubral-pallidolusian atrophy; F, female; GD, Gaucher disease; LAS, Lance-Adams syndrome; M, male; PB, phenobarbital; N/A, not available; PIR, piracetam; PRM, primidone; SEP, somatosensory-evoked potential; TPM, topiramate; VPA, sodium valproate; LEV, levetiracetam; ZNS, zonisamide.

Before PER administration, the clinical data for myoclonus and ADL scores were available in 18 (100%) and 17 (94%) patients, respectively.

After PER administration, we followed up myoclonus score in 17/18 (94%) patients and ADL score in 16/18 (89%) patients. Eight patients lacked SEP data of “before” or “after”. PER concentration was not followed up after administration in one patient (Patient 12).

* Clinically diagnosed with ULD (not on the basis of genetic diagnosis).

** This SEP was evaluated >5 years before PER administration; because the duration from “before” to “after” was very long [more than five years], this patient (Patient 13) was excluded for the subsequent analyses (comparison of SEP data before and after PER treatment).

*** The presence of decrement in amplitude and prolongation of latency after PER treatment is stated for each SEP component. “Temporal dispersion (+)” is stated when the finding was observed in at least one side of the right and left median nerve stimulation.

reflex were reviewed to compare conditions before and after PER administration to clarify also the clinico-electrophysiological impacts of PER treatment on cortical myoclonus (see [Supplementary Fig. 1](#) for data sources). Clinical and electrophysiological data spanning the period 1 to 2 months before PER treatment were evaluated as baseline conditions before PER administration, and parameters after >30 days from PER administration were evaluated as conditions after PER administration. PER blood concentration was measured when the PER dosage was increased and when the PER blood concentration reached the maintenance dosage (according to both treatment responsiveness and side effects). Of the PER concentration data measured, those that were examined (1) after >30 days following the initial PER administration and (2) when the clinical condition of the patient was stable, were used for further analysis. Some patients were treated with enzyme-inducer drugs before the PER administration. However, the dosage of these inducers was not changed during the study period.

2.3. Clinical parameters

To designate the degree of myoclonus, the global impression of disability due to myoclonus was evaluated using myoclonus score from 0 to 4 degrees: absence of myoclonus = 0; mild myoclonus without disturbance of daily activity = 1; moderate, some disturbance of daily activity = 2; severe, clear disturbance of daily activity = 3; marked, causing incapacity = 4 ([Supplementary Table 1](#)). This scale was adopted from a previous study ([Ikeda et al., 1996](#)). Disability in daily life was assessed with the ADL score by interviewing patients or their family members ([Supplementary Table 2](#)) ([Ikeda et al., 1996](#)). The ADL score consisted of the frequency of epileptic seizures, functional disabilities closely associated with myoclonus (i.e., ataxic gait, dysarthria, eating, swallowing, dressing, sleep hygiene, and hand writing), and psychological state. Each parameter was assessed using five grades (none = 0, slight = 1, mild = 2, moderate = 3, severe = 4). The total score (a sum of all points) was calculated for each patient (total score range: 0–36). A 50% reduction in generalized tonic clonic seizures was used as the threshold for a clinically meaningful change of seizures in this ADL score ([Supplementary Table 2](#)).

2.4. Electrophysiological examination

We examined SEP using the Neuropack (Nihon Kohden, Tokyo, Japan). We employed standardized recording conditions used in previous studies for giant SEPs ([Shibasaki et al., 1985](#)). The band-pass filter was set to 0.5–3000 Hz. Reference electrodes were placed on the earlobe ipsilateral to the stimulation side. Recording electrodes were placed on the skin 2 cm posterior to C3/C4 according to the International 10–20 System (C3'/C4') with electrode impedance maintained below 5 k Ω . The median nerve was stimulated at the wrist with the stimulus strength adjusted to approximately 10% above the motor threshold. At least two sessions were required to confirm the reproducibility of SEP waveforms for each side of stimulation. We measured amplitudes and peak latencies of SEPs in each early cortical component (N20, P25, and N33). N20 amplitudes were measured from baseline. P25 and N33 amplitudes were measured from the preceding opposite peak. As indices of cortical excitability in S1 and M1, we evaluated the presence of giant SEP, which was defined as follows; (1) P25 amplitude (measured peak-to-peak between N20 and P25) more than 6.3 μ V or (2) N33 amplitude (measured peak-to-peak between P25 and N33) more than 9.5 μ V ([Shibasaki et al., 1977](#)). We also examined the presence of C-reflex when it was clinically possible, that was confirmed with a latency of 40–55 ms to median nerve stimulation at the wrist ([Sutton and Mayer, 1974](#)).

2.5. Assessments and statistical analyses

We primarily assessed changes in clinical parameters and then SEP components (latency and amplitude) before and after PER administration using Wilcoxon paired t-tests. To clarify the effect of PER on SEP responses, the correlation between changes in amplitude and latency after PER administration was assessed using Pearson correlation analysis. We assessed the tolerability and safety of PER from clinical data including side effects that were evaluated at every visit. The associations between PER dosage and side effects were also assessed.

The secondary assessments were correlations among changes in clinical symptoms, SEP components, and PER concentration analyzed using Pearson correlation coefficient. All statistical analyses were conducted using JMP software (JMP Pro version 12; SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant. To highlight changes in SEP latency, we operationally adopted the side (left or right) showing larger chronological changes of SEP latency in each patient for correlation analysis.

3. Results

3.1. Clinical parameters before and after PER treatment

The mean myoclonus score was 2.8 ± 0.8 before PER administration (range: 1–4) ([Table 1](#)). Seventeen patients had moderate to severe myoclonus even under AED therapy at baseline, whereas remaining one patient (No. 13) had mild myoclonus. The mean ADL score was 13.8 ± 7.9 before PER administration. The ADL scores are described in detail in [Supplementary Table 3](#). The mean PER concentration was 234.3 ± 168.0 ng/mL. The mean myoclonus scores significantly decreased from 2.8 ± 0.8 to 1.8 ± 0.8 ($p < 0.001$); the myoclonus score decreased in 13/17 patients (76%) ([Fig. 1A](#)). None of the patients reported worsening of myoclonus after treatment. Mean ADL score significantly improved from 13.8 ± 7.9 to 10.2 ± 6.7 ($p < 0.001$); the ADL score improved in 15/16 patients (94%). None of the patients exhibited worsening of ADL score after treatment either. Details of ADL scores after PER administration are shown in [Supplementary Table 3](#). During this observation period, generalized convulsive seizures were ameliorated after PER treatment in 5 of 6 (83%) patients, and 2 of them became seizure-free. Of note, remarkable clinical improvement related to myoclonus was reported by patients as follows; (1) Patient 3 was able to eat without assistance (ADL score changed from 18 to 15); (2) it became easier for Patient 2 to get on motor vehicles (ADL score improved from 25 to 18); (3) jumping exercises became possible in Patient 12; and (4) Patient 11 and 14 who were bedridden before PER treatment were able to stand up without assistance. These substantial changes in ADL provided strong supportive information that patients' quality of life (QOL) improved. However, these clinical and subjective improvements were not fully reflected by the myoclonus scores, largely because of the limitation in the score resolution.

3.2. Safety and side effects ([Fig. 2](#))

We commenced with and titrated by low dose of PER, and only mild degrees of various side effects including sleepiness, dizziness, body weight gain, hallucinations, and palpitations were observed in 8 of 18 (44%) at the dose range of 1.5–3.0 mg/day. The most frequent side effect was sleepiness ($n = 5$), followed by body weight gain ($n = 3$), and dizziness ($n = 2$). All of these side effects were tolerable after reducing the dosage of either PER or concomitant medications. Hallucinations immediately disappeared after reducing

the PER dosage (Patient 3). Palpitation was also mild without causing a disabling condition in daily life (Patient 17).

3.3. SEP findings before and after PER treatment

3.3.1. Amplitude findings

Before PER administration, SEP was examined in 15 patients, which revealed giant SEPs in 11 of 15 patients (73%). Of those 15 patients, we recorded SEPs in nine before and after PER administration. In this subset of nine patients (BAFME = 4, ULD = 4, and Gaucher disease = 1), giant SEPs were observed in all patients (Table 1), and the mean amplitudes of P25 and N33 were $13.5 \pm 6.5 \mu\text{V}$ and $21.2 \pm 12.1 \mu\text{V}$ before treatment; and $9.1 \pm 4.5 \mu\text{V}$ and $14.4 \pm 7.1 \mu\text{V}$ after treatment, respectively. Significant decrements in mean SEP amplitudes were observed in both P25 ($p < 0.003$) and N33 ($p = 0.035$) (Fig. 1B). All and eight (89%) patients exhibited a decrement in P25 and N33 amplitudes by at least $1.0 \mu\text{V}$, respectively. The degree of decrements in amplitude was very high in patients with very high SEP amplitudes ($>20 \mu\text{V}$) before PER treatment. C-reflex was observed in 7 of 11 patients (64%) that were examined before treatment. Absence of C-reflex was observed after PER treatment in 3 of 5 patients (60%).

3.3.2. Latency findings

The mean latencies of N20, P25, and N33 were $18.2 \pm 1.6 \text{ ms}$, $23.8 \pm 1.6 \text{ ms}$, and $32.1 \pm 4.0 \text{ ms}$ before treatment; and $18.9 \pm 1.54 \text{ ms}$, $24.7 \pm 1.7 \text{ ms}$, and $33.7 \pm 3.4 \text{ ms}$ after treatment, respectively. After PER administration, a significant prolongation of the mean SEP latency of N20 was observed ($p = 0.007$). Overall

latency change of P25 and N33 after treatment seems to be prolonged, and furthermore, it clearly showed the positive correlation with decreased amplitude (Paragraph 3.4) and the degree of clinical improvement (Paragraph 3.5) as described in the next paragraphs. Several patients showed clear prolonged latencies of in P25 or N33 (Fig. 1C), although statistical significance was not reached in P25 ($p = 0.13$) and N33 ($p = 0.19$).

3.4. Correlations between prolonged latency and decreased amplitude of SEPs (Figs. 3 and 4)

Representative SEP waveforms obtained before and after PER treatments are shown in Fig. 3 (Patient 1). At least P25 and N33 clearly showed decreased amplitudes with prolonged latencies; it may be called as “temporal dispersion” after PER treatment. This phenomenon was classically reported previously, (Shibasaki et al., 1982; Tomoda et al., 1988) and it was observed in six patients (67%) for P25 and eight (89%) patients for N33, at least in one side of the left and right median nerve stimulations. This “temporal dispersion” was more evident in correlation analysis; correlations between decreased amplitude and prolonged latency of SEPs were significant in P25; the smaller the P25 amplitude, the longer the latency (Fig. 4, $p = 0.033$, Pearson correlation coefficient [ρ] = -0.71). This correlation was reproducible in the examination of contralateral side stimulation (Supplementary Fig. 2A-1, $p = 0.018$, $\rho = -0.76$). In contrast, these trends were not evident in N33 (Supplementary Fig. 2B).

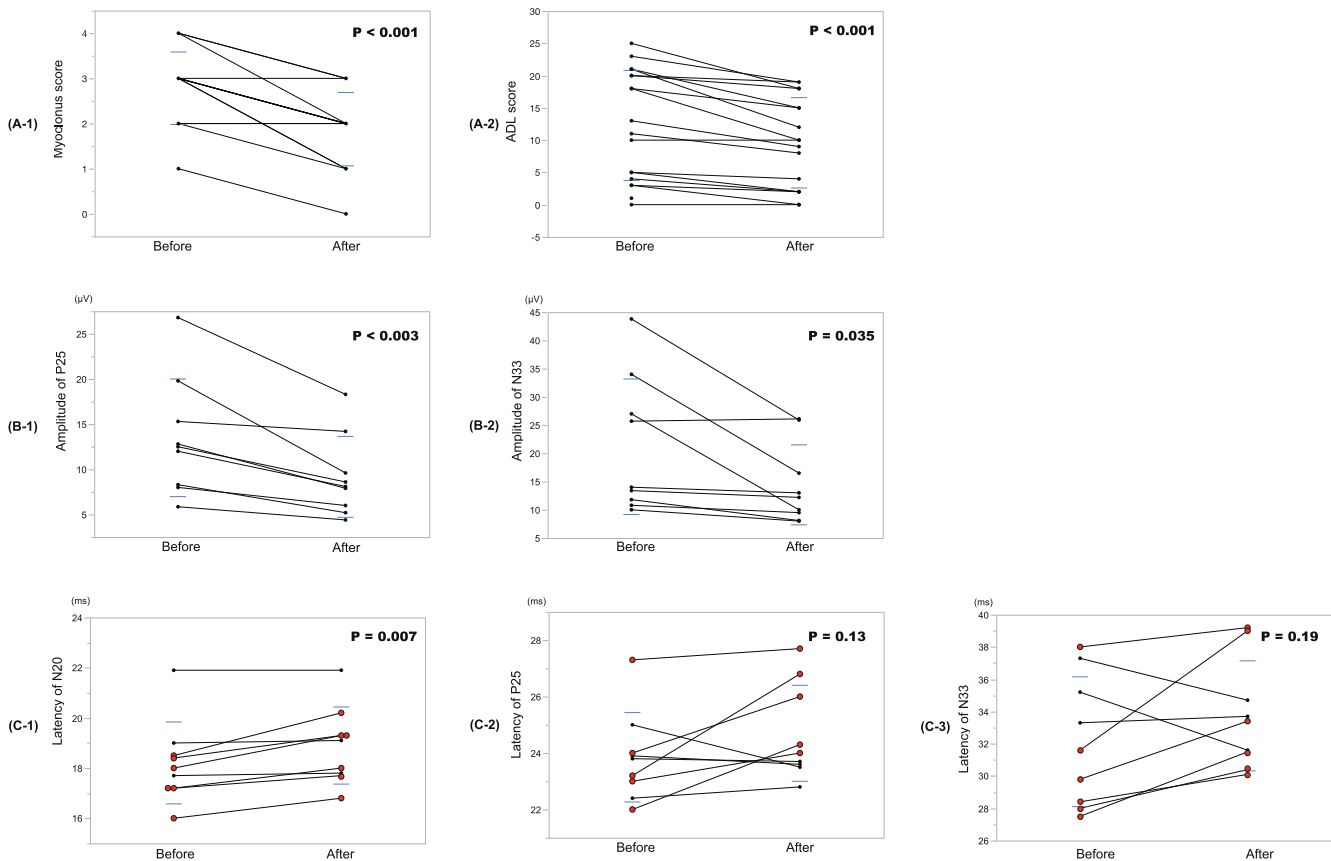


Fig. 1. Changes in clinical parameters and SEP components after PER treatment. (A) Changes in myoclonus (A-1) and ADL (A-2) scores after PER treatment. (B) Changes in SEP amplitudes in P25 (B-1) and N33 (B-2) after PER treatment. (C) Changes in SEP latencies in N20 (C-1), P25 (C-2), and N33 (C-3) after PER treatment. Blue bars indicate standard deviation. Red dots in C-1, C-2, and C-3 indicate the patients whose SEPs clearly showed prolonged latency after PER treatment. SEP, somatosensory-evoked potential; PER, perampanel. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

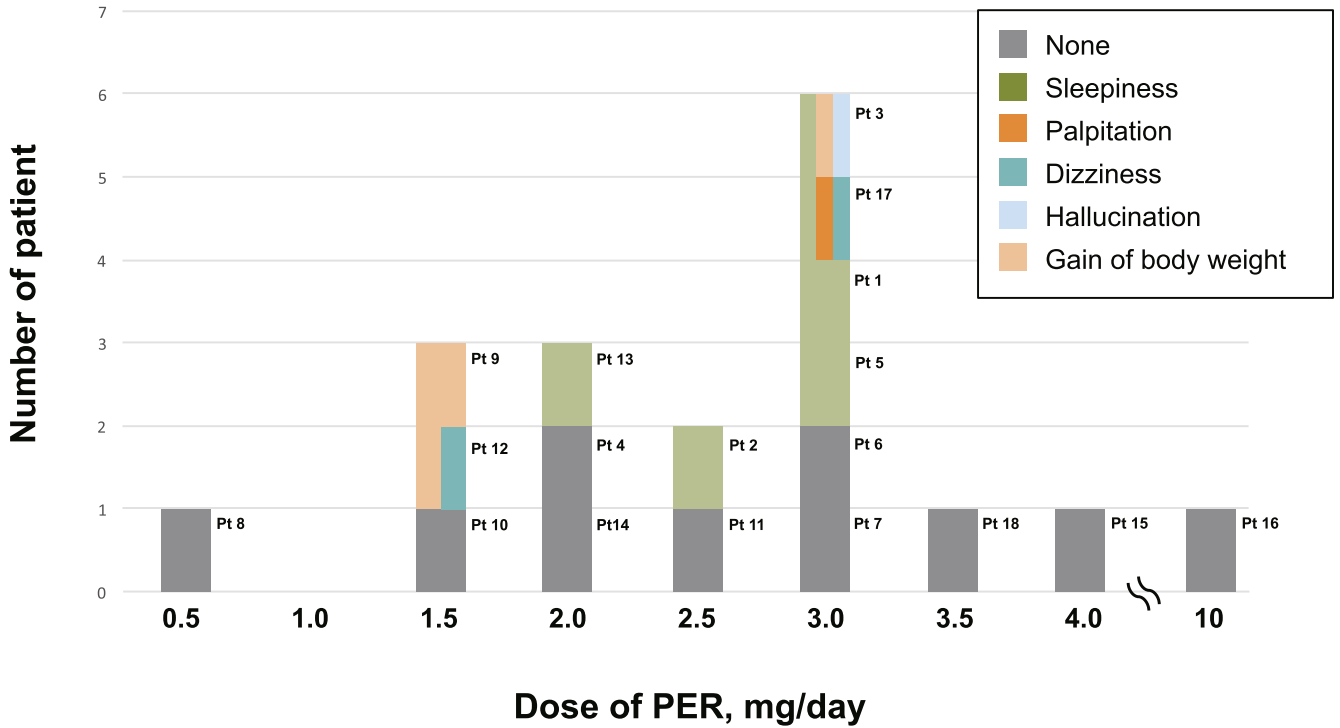


Fig. 2. Side effects according to PER dosage. Distribution of side effects due to PER (perampanel) treatment in accordance with PER daily dosage is illustrated for each patient. Sleepiness (green bar) was the most frequent side effect followed by body weight gain (light orange bar). There were 10 patients (gray bar) without side effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

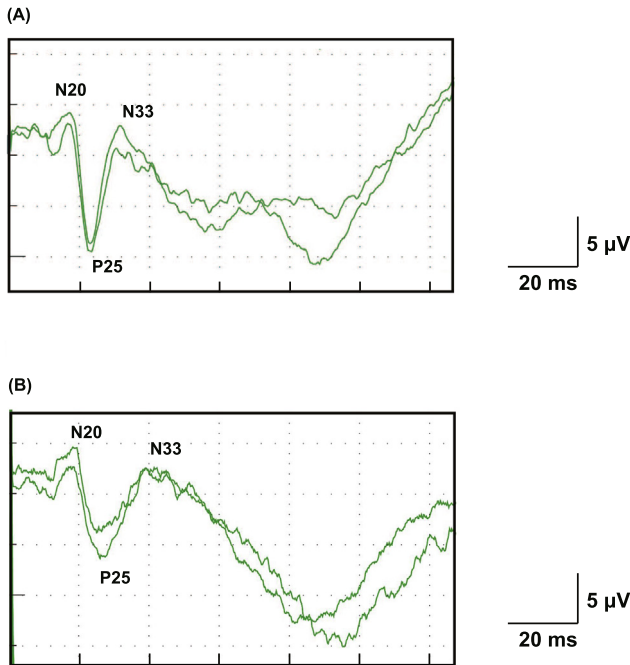


Fig. 3. Representative SEP waveforms. Representative waveforms of SEPs recorded before (A) and after (B) PER treatment to left median nerve stimulation in Patient 1. Decreased amplitude and prolonged latencies (temporal dispersion) are reproducibly observed in P25 and N33, and also in N20 to a lesser degree. SEP, somatosensory-evoked potential; PER, perampanel.

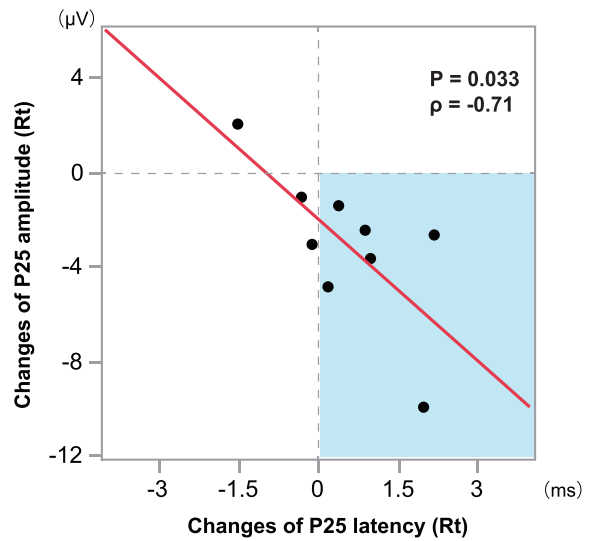


Fig. 4. Correlations between prolonged latency and decreased amplitude of SEP P25 by right median nerve stimulation. Data from nine patients whose SEPs were examined before and after treatment are derived. Dots in the areas highlighted by blue represent SEP changes with “temporal dispersion” (prolonged latency with decreased amplitude of SEPs) due to PER treatment. Significant correlation between prolonged latency and decreased amplitude following PER treatment are visible in P25. ρ , Pearson correlation coefficient; PER, perampanel; SEP, somatosensory-evoked potential. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

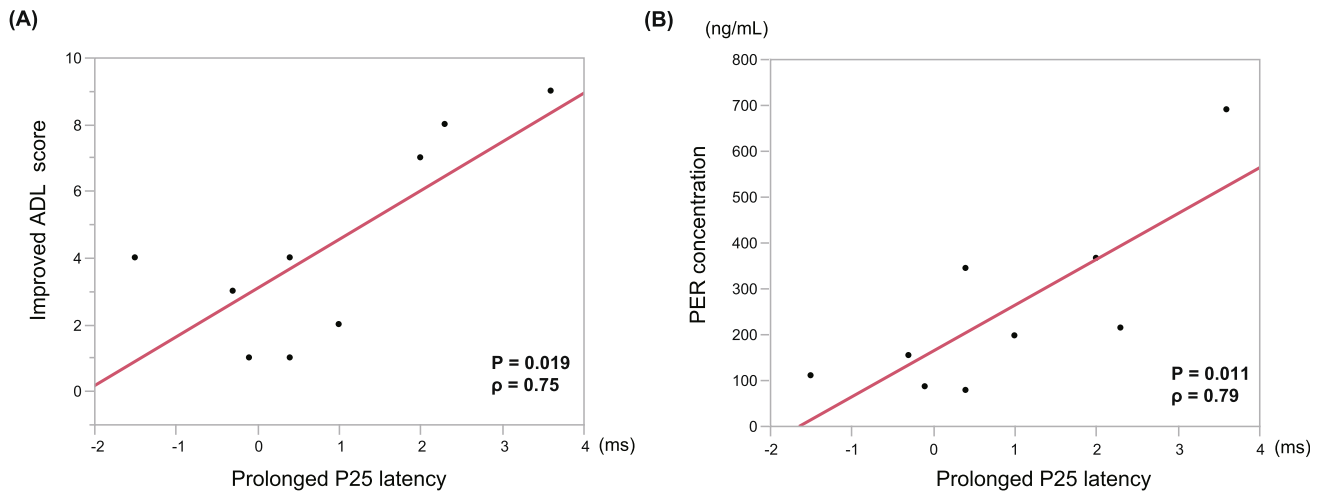


Fig. 5. Correlations among ADL score, PER concentration, and SEP latency. Data from nine patients, whose SEPs were examined before and after treatment, are derived. The changes in clinical parameters from ADL score (A) and PER concentration (B) are shown in correlation analysis with changes in SEP latencies of P25. These correlations are also reproduced in N33 as shown in [Supplementary Fig. 3](#). ρ , Pearson correlation coefficient; ADL, activities of daily life; PER, perampanel; SEP, somatosensory-evoked potential.

3.5. Correlations among clinical scores, PER concentration, and SEP latency/amplitude after PER treatment (Fig. 5)

Correlations between changes in SEP latency and clinical parameters (myoclonus score, ADL score, and PER concentration) were evident as shown in [Supplementary Fig. 3](#). Of those, the correlations were most significant in P25 (Fig. 5). Prolongation of SEP latencies in P25 correlated to improved ADL score following PER treatment ($p = 0.019$, $\rho = 0.75$). This significant correlation was also observed in N33 ([Supplementary Fig. 3B-3](#), $p = 0.025$, $\rho = 0.73$). Correlations were also significant between PER concentration and prolongation of P25 (Fig. 5B $p = 0.011$, $\rho = 0.79$) and between PER concentration and N33 latencies ([Supplementary Fig. 3C-3](#), $p = 0.025$, $\rho = 0.73$).

There were no significant correlations between the degree of prolongation of SEP latencies (N20, P25, and N33) and the degree of improvement of myoclonus scores, whereas that of N33 tended to correlate with that of myoclonus scores ([Supplementary Fig. 3A-3](#), $p = 0.052$, $\rho = 0.66$). The prolongations of N20 tended to correlate with changes in ADL score ([Supplementary Fig. 3B-1](#), $p = 0.068$, $\rho = 0.63$), although this was not statistically significant. The correlation between PER concentration and the prolongation of N20 was not significant ([Supplementary Fig. 3C-1](#), $p = 0.25$, $\rho = 0.43$).

Overall, with regard to changes in the three clinical parameters, the latency and amplitude changes in P25 and N33 were similar but differed substantially from those of N20. Changes in P25 and N33 SEP amplitudes were not significantly correlated with changes in clinical parameters.

4. Discussion

For patients with seizures and medically refractory cortical myoclonus from variable backgrounds, this is the first report (1) to elaborate clinical effects of PER on cortical myoclonus for dose, etiology and SEP findings, and (2) to evaluate the clinico-electrophysiological impacts of adjunctive PER. This study also contributes to elucidate a possible biomarker for the effectiveness and dose management of PER in cortical myoclonus in accordance with the changes in SEP components. Namely, it is most likely a prolonged and decreased giant SEP of P25.

Clinically important several key findings emerged from our study. First, a low dose of PER dramatically improved patients' myoclonus and ADL. Second, unique SEP findings under PER treatment were observed after PER treatment in our particular patients

(BAFME, ULD, and Gaucher disease) as follows. After PER treatment, a significantly decreased SEP amplitude was observed in giant SEPs (P25 and N33). In addition, prolonged SEP latencies (P25 and N33) apparently varied among patients, but it clearly correlated with the degree of ADL improvement and PER concentration for the particular patients. This finding suggests the “temporal dispersion” of SEP components after PER therapy in our study. Especially, the correlations between decreased SEP amplitude and prolonged latency were noteworthy because these significant correlations were observed only in SEP components of P25 (and N33 to a lesser degree) that represented the “giant SEPs.” The importance of this particular SEP component is highlighted in the correlations between prolongation of latency and positive clinical outcomes (ADL score and PER concentration). Given these contributions, P25 and N33 are components that reasonably represent the impact of PER on cortical myoclonus.

4.1. Newly elaborated findings

Several previous studies have reported the efficacy of PER for PME; however, these studies were limited in the number of patients, variety of disease type, and systematic assessment of myoclonus (Goldsmith and Minassian, 2016; Crespel et al., 2017; Shirashi et al., 2017; Hu et al., 2018). Our study assessed the changes in the types of clinical parameters (myoclonus and ADL scores, and PER concentration) and SEP components and revealed that low dose PER was sufficient to reduce cortical myoclonus regardless of etiology. Of note, the PER dosage in our study (mean dose: $3.2 \text{ mg} \pm 2.1 \text{ mg/day}$) was much lower than that in previous studies (mean dose: 6 mg/day) (Crespel et al., 2017; Gil-López et al., 2018). This may be because all our patients (Japanese) had rather better controlled seizures and low body weights that were acceptable given the dose-dependent effects (Kramer et al., 2014). Based on these findings, the optimal PER dosage may vary among individuals.

4.2. How does a small dose of PER suppress cortical myoclonus very well?

The SEP components of P25 and N33, but not N20, in patients with cortical myoclonus usually represent “giant” SEPs (Shibasaki et al., 1985). Giant SEPs reflect epileptic hyperexcitability of S1-M1 (Shibasaki et al., 1985). Indeed, giant SEP amplitude was reportedly reduced by conventional AED treatment in the last

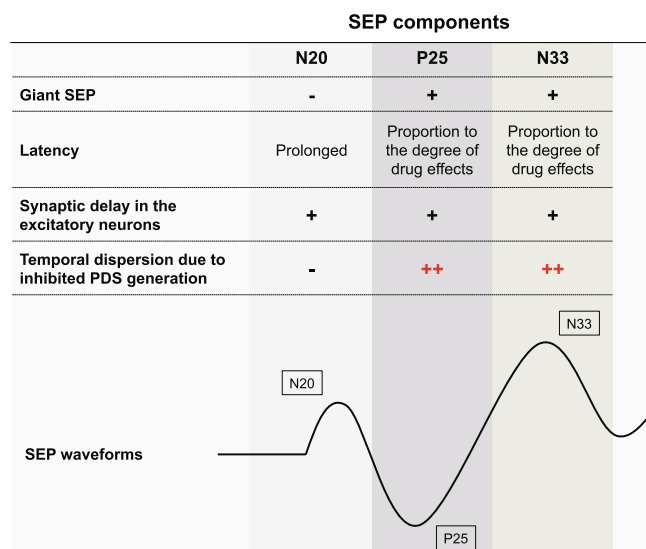


Fig. 6. The hypothesis of the mode of action of perampanel on giant SEP components in cortical myoclonus. Differences between earlier (N20) and later parts of SEP components (P25 and N33) are shown. Giant SEP is observed in P25 and N33 but not in N20. Temporal dispersion is observed for P25 and N33 but not N20. SEP, somatosensory-evoked potential. The details are described in the “Discussion.”

(Shibasaki et al., 1985). A long-term observational study reported a gradual, but much lesser decrease of SEP amplitude in ULD along with a self-limited clinical course (Kobayashi et al., 2014). The N20 component may remain normal as the source of N20 is proposed to be thalamocortical projections or excitatory postsynaptic potentials (EPSPs) whereas P25 and N33 components are enlarged due to enhanced postsynaptic cortical potentials (Shibasaki et al., 1985). The cortical generators of N20 and P25/N33 differ spatially. The generator of tangential N20 arises from the posterior bank of the central sulcus whereas radial components of P25 and N33 arise from the crown of the postcentral gyrus (Allison et al., 1991; Ikeda et al., 1995). P25 could represent M1 excitability at least partly because the generator of P25 was partly located in the motor and sensory areas (Mima et al., 1998). Given the significant decrease in P25 amplitudes in our study, it is reasonable that PER reduces epileptic hyperexcitability of M1. This hypothesis may be partly supported by our results that the C reflex disappeared in some patients (although the number of patients evaluated was limited).

The SEPs under PER treatment showed not only decreased amplitude but also prolonged latency. This “temporal dispersion” was not notable in any AEDs other than PER in the reported SEPs (Rothwell et al., 1984). Typically, decreased cortical activity induced by drugs is represented mainly by reduced SEP amplitude, and no or little latency (Carenini et al., 1988). The pharmacological differences in the sites of action between PER and other AEDs are worth discussing, as PER is the only AED that suppresses AMPA receptor activity in the postsynaptic neurons whereas other AEDs such as sodium channel blockers suppress intraneuronal conduction outside synaptic transmission, or presynaptic conduction (Ledingham and Patsalos, 2013; Schmidt and Schachter, 2014). Epileptic ictal and interictal activities are originally generated by paroxysmal depolarization shifts (PDS) that are regarded as abnormal, giant EPSPs (Johnston and Brown, 1981; Goldensohn et al., 1986). Characteristics of SEP components in cortical myoclonus and the effects of PER on them are summarized in Fig. 6.

This action can be electrophysiologically examined based on decrement in SEP amplitude. In contrast, PER could directly affect PDS because PER acts on postsynaptic neurons as a selective non-competitive AMPA receptor antagonist that suppresses neuronal hyperexcitability by reducing Ca^{2+} inflow (Hanada et al., 2011;

Rajasekaran et al., 2012). Thus, PER suppresses the generation of synchronized firing (PDS) by blocking postsynaptic AMPA receptors (Rogawski, 2011), and also presumably lead to desynchronization of PDS generation (Traub et al., 1993; Rogawski, 2013) as the temporal dispersions. These mechanisms are plausible given that myoclonus was clinically improved by PER, as cortical myoclonus is considered an epileptic myoclonus and is caused by the excessive synchronization of abnormal firing of motor neurons (Ikeda et al., 1990). Namely, it is acceptable that the enlarged SEP components such as P25 and N33 showed temporal dispersions, but not for non-enlarged component as N20. Hence, we suggest that PER inhibited and dispersed epileptic cortical hyperexcitability with hypersynchronization in M1, leading to myoclonus attenuation. To provide further support for our hypothesis, future studies are necessary to investigate cortical neuronal firing, reflected by high frequency band activity (Coppola et al., 2005; Endisch et al., 2016), in accordance with changes in cortical components (P25 and N33) and cortical myoclonus treated by PER. EEG/EMG coherence analysis is also of interest given that it provides the most important information to distinguish between cortical and other types of myoclonus (Shibasaki, 1988).

4.3. Limitations

(1) Due to the retrospective uncontrolled case accumulation of this study with limited follow-up period, several factors may have affected clinical outcomes. This condition could not rule out the placebo effects and fluctuation in the disease. The study population was limited given the heterogeneous group of cases affected by cortical myoclonus resulting from diverse etiologies. There were missing data. Measurement bias, including the presence of partly self-measurement, should also be acknowledged. (2) The number of patients who underwent SEPs evaluations both before and after PER treatments was still limited. However, our particular SEP findings, increased temporal dispersions, were clearly reproducible in the present study at least in patients with BAFME and ULD. To address these limitations, it is critical to expand the number of patients to validate the present finding in a long-term follow up with inter- and intra-individual variation in PER dose. Applying statistical analysis adjusted by multiple testing to this data will elucidate the meaning of temporal dispersion of giant SEP components.

4.4. Conclusion

We have extensively evaluated the clinico-electrophysiological impacts of PER on patients with seizures and cortical myoclonus. Low-dose PER substantially improved myoclonus, QOL, and seizures. Temporal dispersion of early cortical components of giant SEPs (P25 and N33, the latter of which arose at least partly from M1), suggests that PER finally reduced the degree of synchronized discharges in the postsynaptic neurons in the motor efferent pathways.

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Disclosure of Conflicts of Interest

This study was completed for data acquisition and analysis until May 2018 at which time the department of Epilepsy, Movement

Disorders and Physiology was an endowment department supported by a grant from GlaxoSmithKline K.K., NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd. Since June 1st 2018, this department has changed to the Industry-Academia Collaboration Courses.

The remaining authors have no conflict of interest.

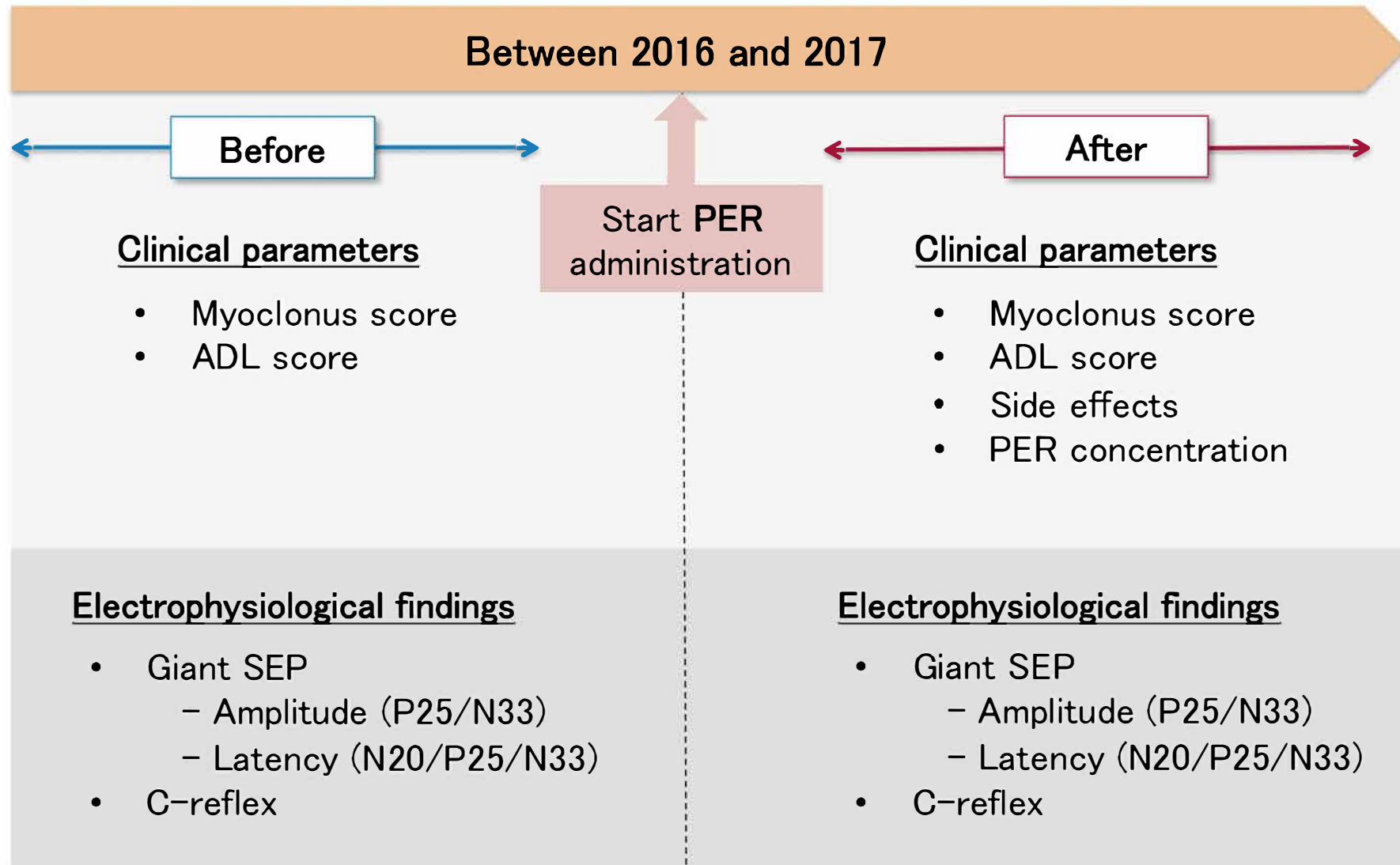
Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2019.07.006>.

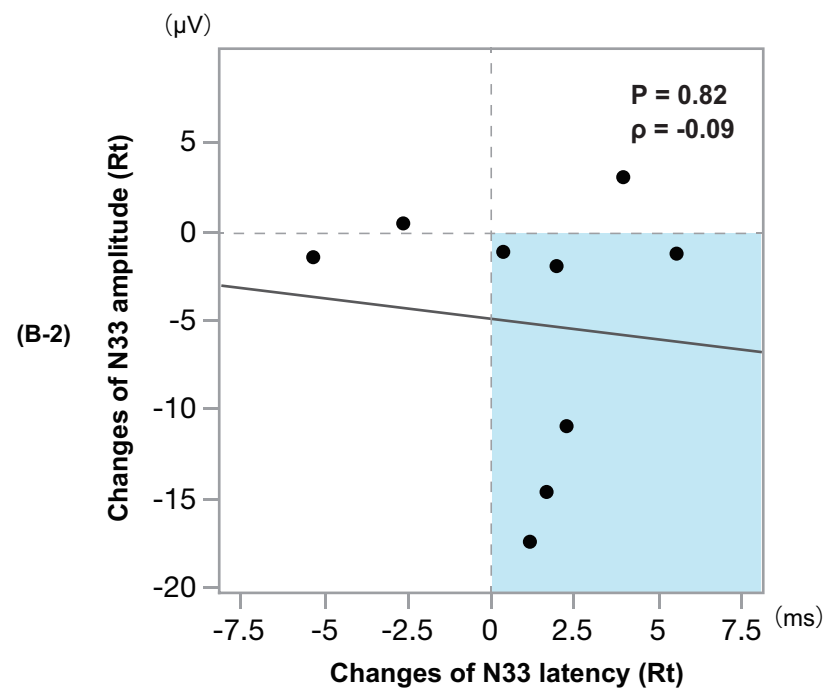
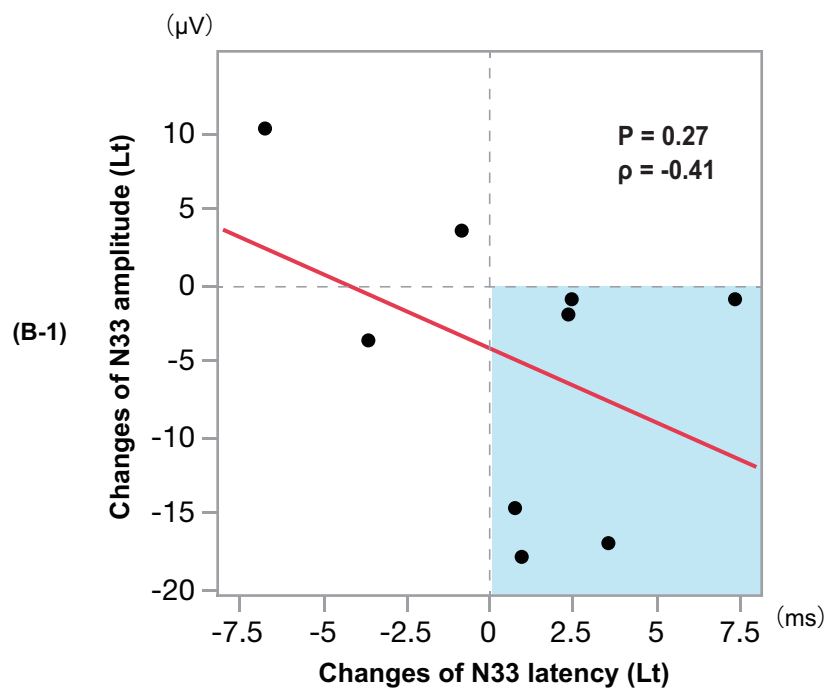
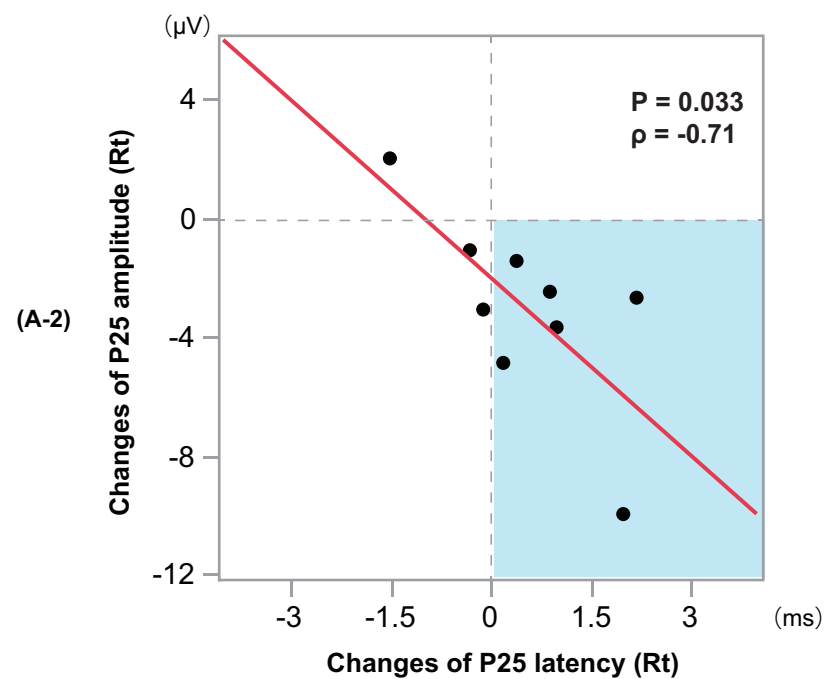
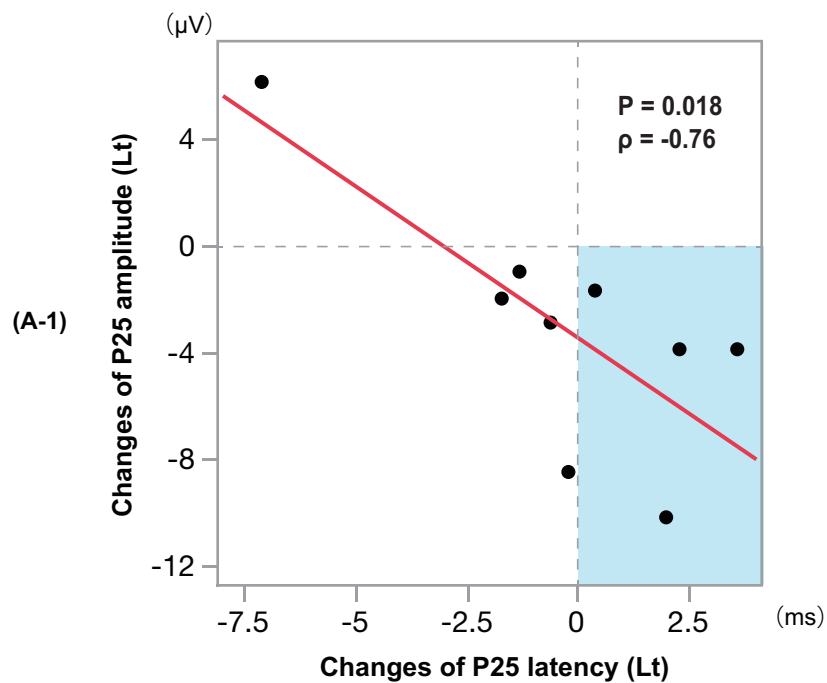
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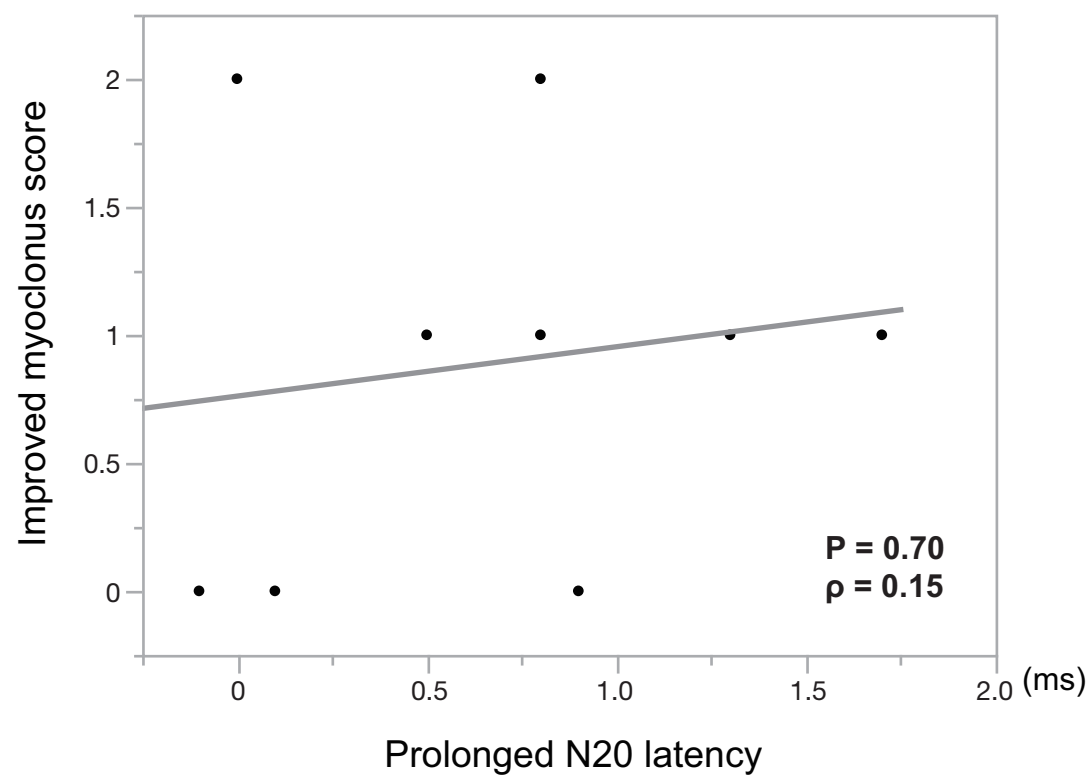
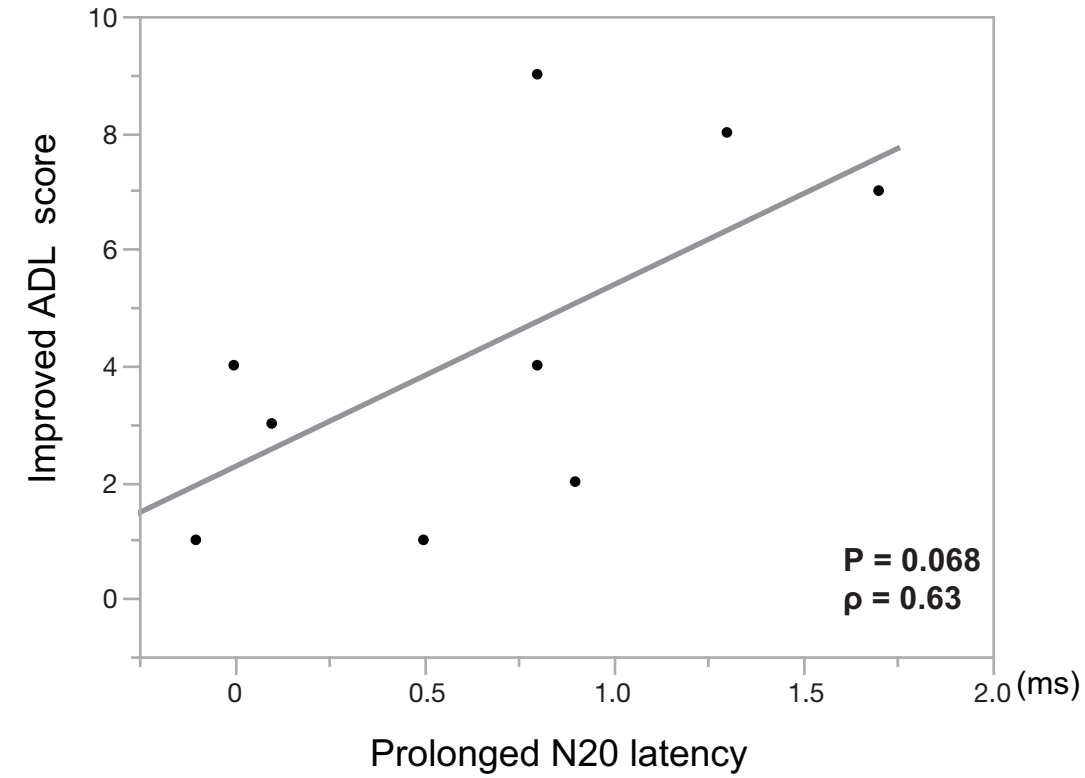
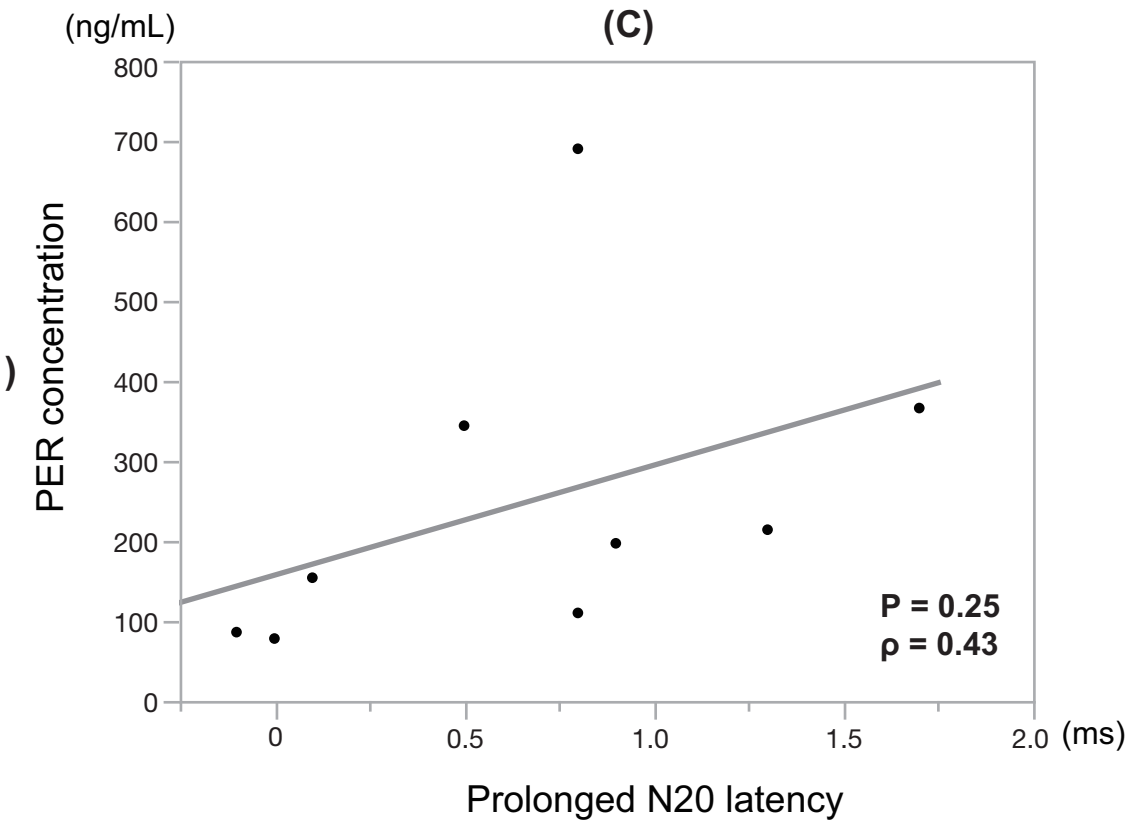
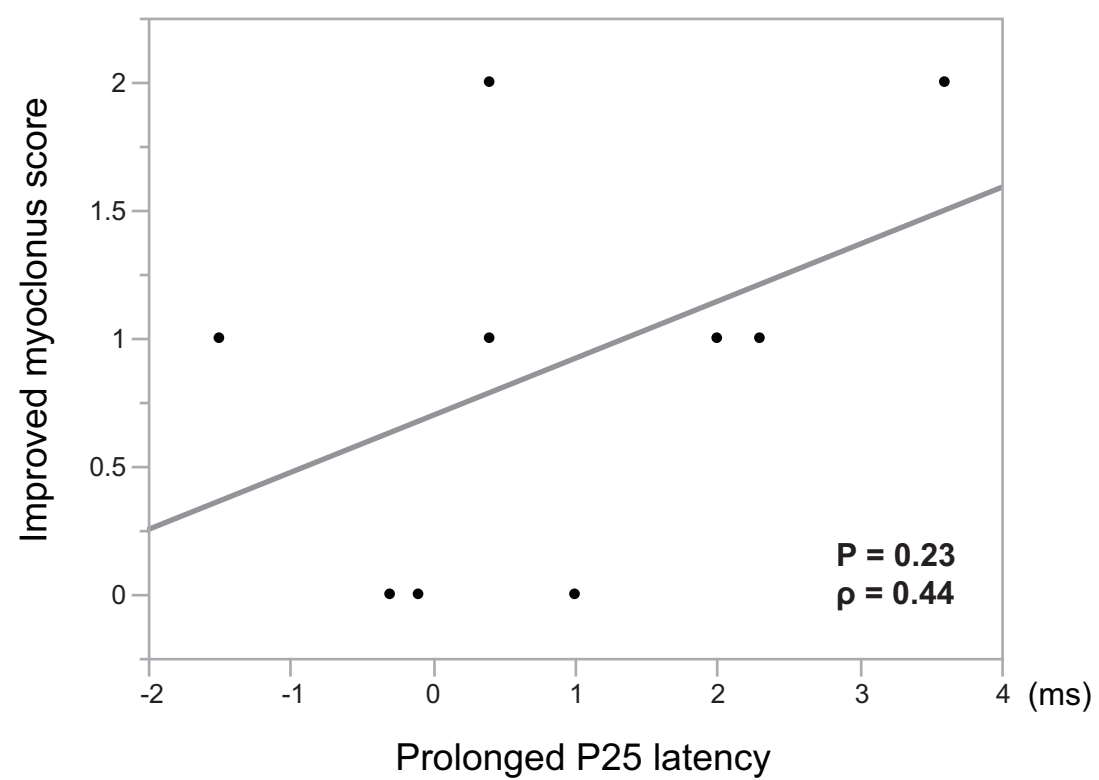
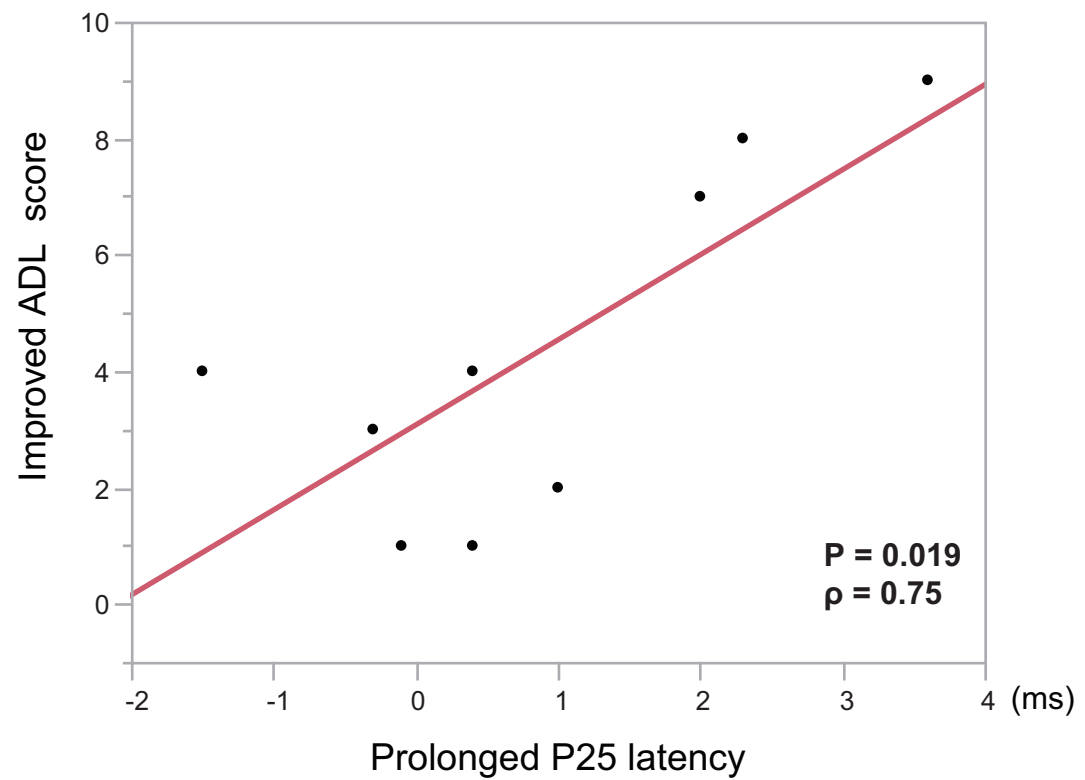
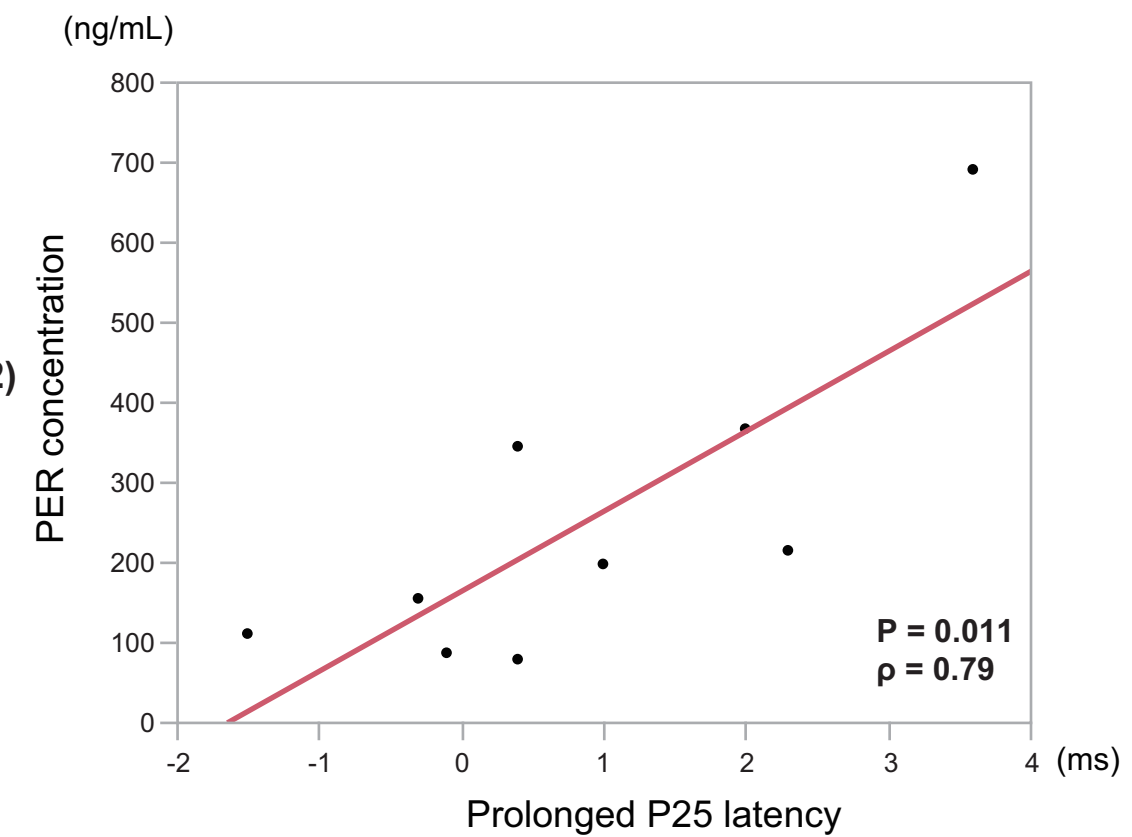
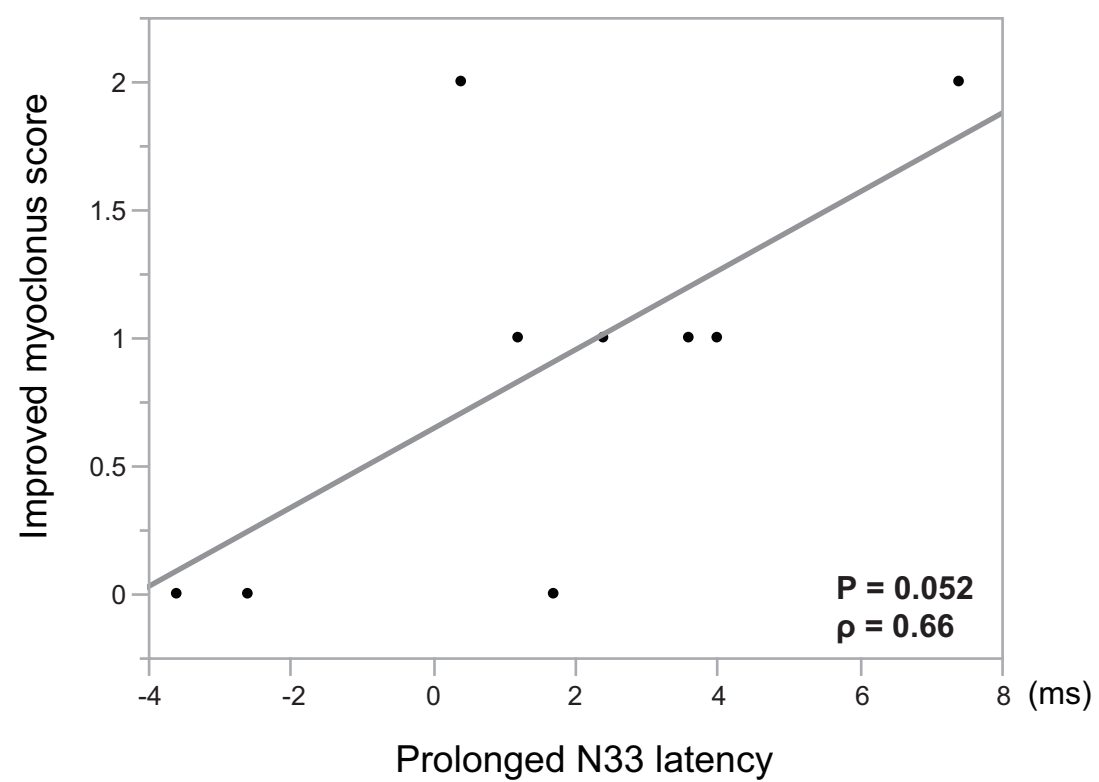
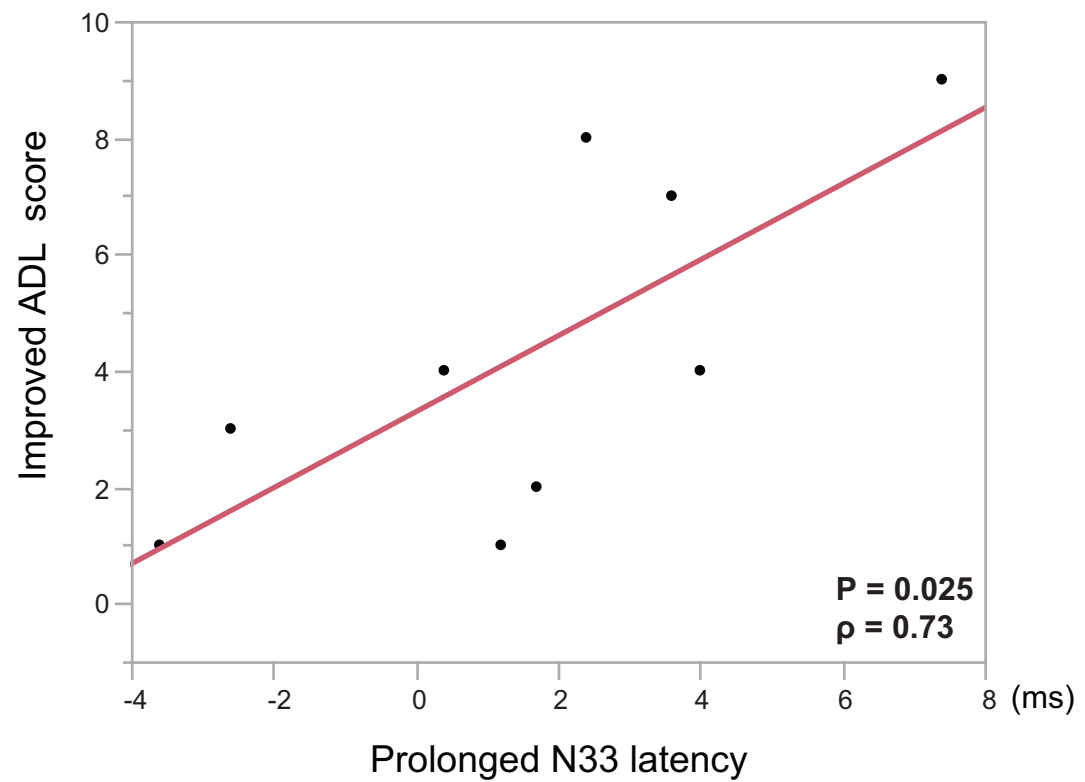
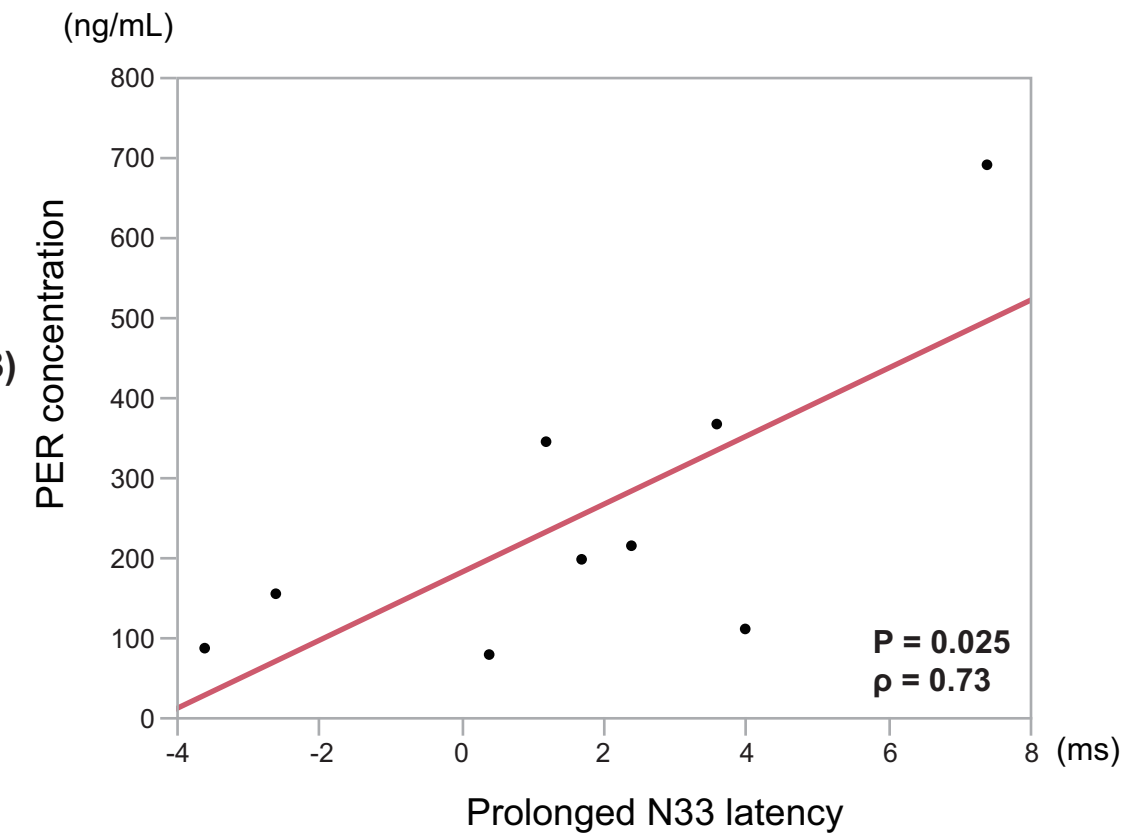
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Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3**(A)****(A-1)****(B)****(B-1)****(C)****(C-1)****(A-2)****(B-2)****(C-2)****(A-3)****(B-3)****(C-3)**

Supplementary Table 1. Myoclonus score.

Severity	Score	Evaluation criteria
Marked	4	Causing incapacity
Severe	3	Clear disturbance of daily activity
Moderate	2	Some disturbance of daily activity
Mild	1	Mild myoclonus without disturbance of daily activity
Absence	0	Absence of myoclonus

This score is adopted from Ikeda A. et al. *Mov Disord.* 1996 Nov;11(6):691-700.

Supplementary Table 2. ADL score.

Symptom	Severity	Score	Evaluation criteria
Neurological symptoms			
Generalized convulsion	Severe	4	Determined by the investigator
	Moderate	3	
	Mild	2	
	Slight	1	
	None	0	
Ataxic gait	Severe	4	Unable to walk
	Moderate	3	Able to walk with assistance
	Mild	2	Severely abnormal gait
	Slight	1	Mildly abnormal gait
	None	0	Normal
Dysarthria	Severe	4	Almost unable or unable to speak
	Moderate	3	Very difficult to be heard
	Mild	2	Difficult to understand what the subject is talking
	Slight	1	Slightly difficult to be heard but talks normally
	None	0	Normal
Disability in daily life			
Eating	Severe	4	Needs assistance

	Moderate	3	Able to eat only foods that can be pinched with the fingers
	Mild	2	Able to use chopsticks, but Unable to cut
	Slight	1	Able to eat by themselves
	None	0	Normal
Swallowing	Severe	4	Unable to swallow fluid foods and drink
	Moderate	3	Unable to swallow solid foods
	Mild	2	Is often choked with foods and finds it difficult to swallow
	Slight	1	Is sometimes choked with food
	None	0	Normal
Dressing	Severe	4	Unable to dress
	Moderate	3	Needs assistance for most of the part
	Mild	2	Partly needs assistance
	Slight	1	Clumsy, but can dress by themselves
	None	0	Normal
Hygiene	Severe	4	Needs complete assistance
	Moderate	3	Needs assistance for most of the part
	Mild	2	Partly needs assistance
	Slight	1	Clumsy, but can perform activities by themselves
	None	0	Normal
Hand writing	Severe	4	Unable to hold a pen

	Moderate	3	Unable to read all the letters
	Mild	2	Unable to read letters for most of the part
	Slight	1	Partly unable to read letters
	None	0	Normal
Psychological state			
Sleep disturbance	Severe	4	Determined by the investigator
	Moderate	3	
	Mild	2	
	Slight	1	
	None	0	
Total score (range)		0 – 36	

Supplementary Table 3. ADL score before and after PER treatment.

Pt No.	Generalized convulsion		Ataxic gait		Dysarthria		Eating		Swallowing		Dressing		Hygiene		Hand writing		Psychological state		Total score		
	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	
1	2	0	4	4	1	1	1	1	1	1	3	2	4	2	1	0	4	1	21	12	
2	0	0	4	3	3	2	4	2	2	1	3	3	4	4	2	1	3	2	25	18	
3	0	0	4	4	3	2	2	1	2	1	1	1	1	1	2	2	3	3	18	15	
4	2	1	4	4	2	1	1	1	1	1	3	3	4	4	3	3	3	1	23	19	
5	1	0	4	3	0	0	3	2	0	0	2	2	3	2	4	0	1	1	18	10	
6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7	0	0	3	3	2	2	1	1	1	1	1	1	1	1	1	1	0	0	10	10	
8	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	1	N/A	0	N/A	1	N/A	
9	0	0	1	1	0	0	2	1	1	0	0	0	0	0	1	0	0	0	5	2	
10	0	0	0	0	0	0	1	1	0	0	0	0	0	0	2	1	0	0	3	2	
11	0	0	3	2	3	1	1	1	0	0	0	0	1	1	3	2	2	2	13	9	
12	0	0	2	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	4	2	
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	3	0	
14	2	2	2	2	2	1	2	2	3	1	2	2	1	2	3	3	3	3	20	18	
15	2	1	3	3	2	2	2	2	2	2	3	3	2	2	4	4	0	0	20	19	
16	0	0	4	3	1	1	4	2	1	0	3	3	3	3	2	1	3	2	21	15	

17	0	0	2	1	2	1	1	1	1	1	1	1	1	1	2	1	1	1	11	8
18	2	1	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	1	5	4

Abbreviation: ADL, activities of daily life; PER, perampanel; N/A, not available.