Amplitude of Somatosensory Evoked Potentials (SEPs) in Short-Latency SEPs Condition is 80% of that in Giant SEPs

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Research Article

Abstract

The recording conditions of somatosensory evoked potentials (giant SEPs) are different from those of short-latency SEPs (SSEPs). We investigated the waveform characteristics obtained for each condition. Forty-eight upper limbs of 24 adult normal subjects (12 males, age 35.5 ± 9.7 years (mean ± SD)) were investigated. The main differences in recording conditions were reference electrodes (giant SEPs: the earlobe electrode ipsilateral to the stimulated limb, SSEPs: Fz), stimulus rate (1 Hz, 5 Hz), and bandpass filter (1 Hz−1 kHz, 20 Hz−3 kHz). SEPs were elicited by unilateral percutaneous electrical stimulation of the median nerve at the wrist. The amplitudes of N20o−N20 and N20−P25 were significantly larger in the giant SEP condition than in the SSEP condition (p<0.001). The mean + 3SD of N20−P25 amplitude was 10.0 µV in the giant SEP condition and 7.8 µV in the SSEP condition. The N20−P25 amplitude was significantly correlated between the giant SEP and SSEP conditions (R=0.64, p<0.001). Thus, the amplitude of SEPs in the SSEPs condition is equivalent to 80% of that in the giant SEPs condition. The information is useful for detecting cortical hyperexcitability in various neurological disorders including myoclonic epilepsy.

Introduction

Somatosensory evoked potentials (SEPs) are used to evaluate the sensory pathway through the peripheral sensory nerve, spinal cord, and cortical primary somatosensory area [1]. Increased amplitude of cortical components (giant SEPs) with enhanced long-loop reflex (C reflex) is observed in epilepsy syndrome with cortical myoclonus, reflecting the hyperexcitability of the somatosensory areas [2−9]. In epilepsy syndrome with cortical myoclonus, evaluation of giant SEPs is useful for the diagnosis and management of the disease. The recording condition of giant SEPs [5, 7, 8] is different from that of short-latency SEPs (SSEPs) [10].

We investigated the correlation of waveform characteristics obtained for each condition to provide useful information for clinical practice. Part of this manuscript was presented in the Asian and Oceanian Epilepsy Congress in 2021, Fukuoka, Japan, in an abstract form.

Methods

Participants

A total of 24 healthy adult subjects (12 males, age 35.5 ± 9.7 years (mean ± SD)) without any neurological diseases were included. Their 48 upper limbs were evaluated. All participants provided written informed consent based on the research protocol approved by the Bioethics Committee of National Hospital Organization Utano National Hospital. All experiments of this study were performed in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines and the Declaration of Helsinki. The study population is the same as the control group in our previous publication [11].

SEP recording

SEPs were recorded by stimulating the median nerve at the wrist. In each subject, both conditions of SSEPs and giant SEPs [5, 7, 10] were recorded in a shielded room on the same day (Fig. 1). In giant SEPs condition, the C reflex was recorded by a pair of disc electrodes placed on the both abductor pollicis brevis muscles, and the subjects were instructed to keep their hands relaxed. The waveform parameters were determined by agreement of board-certified clinical neurophysiologists (A.D., Y.D., and M.K.).

Statistics

The variables of N20−P25 amplitude on the giant SEPs condition did not exhibit a normal distribution as per the Kolmogorov−Smirnov test; thus, the results of parametric tests were confirmed by non-parametric tests using SPSS statistical software (version 27; IBM Japan, Tokyo, Japan). The significance level was set at $p=0.05$ for group comparison and $p=0.01$ for correlation analyses.

Results

Comparison of SEP amplitudes

The amplitudes of N20o−N20 and N20−P25 were significantly larger in the giant SEP condition than in the SSEP condition ($p<0.001$; Table 1, Fig. 2). The mean + 3SD of N20−P25 amplitude was 10.0 μV in the giant SEPs condition and 7.8 μV in the SSEPs condition. The C-reflex was not elicited. Females showed longer latency of P25 and N30 and higher amplitudes of P25−N30 than did males (Table 2). The latency of N20o and N20 was shorter with stimulation on the dominant side than on the non-dominant side (Table 3).

<p style="text-align:center">Table 1
Amplitude measures of each condition (μV)</p>

	Giant SEPs	SSEPs	Ratio*	p^a
N20o−N20				
mean ± SD	4.2 ± 1.8	1.9 ± 0.8	45%	p<0.001
mean + 2SD	7.8	3.5	45%	
mean + 3SD	9.6	4.3	45%	
N20−P25				
mean ± SD	4.6 ± 1.8	3.5 ± 1.4	76%	p<0.001[b]
mean + 2SD	8.2	6.4	78%	
mean + 3SD	10.0	7.8	78%	
P25−N30				
mean ± SD	3.0 ± 1.8	3.0 ± 1.5	100%	n.s.
mean + 2SD	6.6	6.0	91%	
mean + 3SD	8.4	7.5	89%	

SEPs: somatosensory evoked potentials. SSEPs: short-latency SEPs. *: Ratio of amplitude (SSEPs/Giant SEPs). a: Paired t-test. b: Confirmed by Wilcoxon's signed rank test (p<0.001). n.s.: Not significant.

Table 2
Group comparison of waveform measures between males and females (mean ± SD)

	Male	Female	p*
Age (years)	37.0 ± 11.4	33.9 ±7.4	n.s.
SSEPs, latency/height (msec/m)			
N20o	9.08 ± 0.44	9.12 ± 0.54	n.s.
N20[b]	11.12 ± 0.35	11.22 ± 0.45	n.s.
P25[c]	13.53 ± 1.20	13.88 ± 1.54	n.s.
N30	18.62 ± 1.30	19.87 ± 1.77	0.009
SSEPs, amplitude (μV)			
N20o−N20	1.88 ± 0.90	1.95 ± 0.71	n.s.
N20−P25	3.38 ± 1.47	3.63 ± 1.41	n.s.
P25−N30	2.57 ± 1.51	3.48 ± 1.31	0.033
Giant SEPs, latency/height (msec/m)			
N20o	8.30 ± 0.69	8.00 ± 0.53	n.s.
N20	11.18 ± 0.52	11.21 ± 0.76	n.s.
P25	14.26 ± 1.11	15.05 ± 1.10	0.020
N30	18.59 ± 2.11	19.67 ± 1.36	0.044
Giant SEPs, amplitude (μV)			
N20o−N20	4.05 ± 1.54	4.44 ± 1.92	n.s.
N20−P25	4.42 ± 1.79	4.83 ± 1.80	n.s.[a]
P25−N30	2.89 ± 1.58	3.09 ± 2.01	n.s.

SEPs: somatosensory evoked potentials. SSEPs: short-latency SEPs. *: Unpaired t-test. n.s.: Not significant. a: Confirmed by Mann-Whitney U test (n.s.). Significantly correlated with age (b: R=0.543, p<0.001; c: R=0.556, p<0.001).

Table 3

Pairwise comparison of waveform measures between dominant and non-dominant side stimulation (mean ± SD)[a].

	Dominant	Non-dominant	p*
SSEPs, latency/height (msec/m)			
N20o	8.96 ± 0.42	9.24 ± 0.52	0.016
N20	11.18 ± 0.45	11.16 ± 0.36	n.s.
P25	13.83 ± 1.42	13.57 ± 1.35	n.s.
N30	19.34 ± 1.78	19.15 ± 1.54	n.s.
SSEPs, amplitude (μV)			
N20o−N20	2.01 ± 0.89	1.82 ± 0.71	n.s.
N20−P25	3.46 ± 1.28	3.55 ± 1.60	n.s.
P25−N30	2.90 ± 1.29	3.15 ± 1.65	n.s.
Giant SEPs, latency/height (msec/m)			
N20o	8.15 ± 0.54	8.15 ± 0.71	n.s.
N20	11.02 ± 0.66	11.37 ± 0.60	0.019
P25	14.64 ± 1.19	14.67 ± 1.15	n.s.
N30	19.49 ± 2.12	18.77 ± 1.47	n.s.
Giant SEPs, amplitude (μV)			
N20o−N20	4.14 ± 1.71	4.35 ± 1.79	n.s.
N20−P25	4.89 ± 1.96	4.37 ± 1.59	n.s.[b]
P25−N30	3.11 ± 1.64	2.87 ± 1.96	n.s.

SEPs: somatosensory evoked potentials. SSEPs: short-latency SEPs. *: Paired t-test. n.s.: Not significant. a: There was one left-handed male subject and his data were adjusted; there were no ambidextrous subjects. b: Confirmed by Wilcoxon signed-rank test (n.s.).

Correlation analysis of N20−P25 amplitude between recording conditions

The N20−P25 amplitude showed a significant linear correlation between the giant SEPs and SSEPs conditions (R=0.64, p<0.001). Curve-fit analysis showed that the growth model was more suitable than the linear model, and 10 μV for the giant SEPs condition was equivalent to 8.0 μV for the SSEPs condition (Table 4, Fig. 3).

Table 4
Results of curve-fitting model analysis

Model	R	p	Equation
Linear	0.641	<0.001	$Y = 1.827 + 0.799X$
Linear (natural logarithmic transformation of Y)[a, b]	0.660	<0.001	$\ln(Y) = 0.795 + 0.188X$
Logarithmic	0.616	<0.001	$Y = 2.112 + (2.194 \times \ln(X))$
Inverse	0.498	<0.001	$Y = 5.853 - 3.296/X$
Quadratic	0.644	<0.001	$Y = 1.380 + 1.089X - 0.040X^2$
Cubic	0.644	<0.001	$Y = 1.540 + 0.917X + 0.010X^2 - 0.004X^3$
Compound	0.660	<0.001	$Y = 2.215 \times (1.207^X)$
Power	0.668	<0.001	$Y = 2.298 \times (X^{0.542})$
Sigmoid	0.561	<0.001	$Y = e^{(1.769 - 0.848/X)}$
Growth	0.660	<0.001	$Y = e^{(0.795 + 0.188X)}$
Exponential	0.660	<0.001	$Y = 2.215 \times e^{0.188X}$
Logistic[c]	0.661	<0.001	$Y = 1/(0.045 + (0.419 \times (0.790^X)))$

Variables are N20−P25 amplitude on X: short-latency somatosensory evoked potentials (SSEPs) and Y: giant SEPs conditions. a: Same as the growth model. b: ln(Y) can be assumed to follow a normal distribution, as per the Kolmogorov−Smirnov test. c: The most suitable upper limit is 22.

Discussion

To the best of our knowledge, this is the first study to compare SSEPs and giant SEPs. The current study showed that N20o−N20 and N20−P25 amplitudes were significantly different between the SSEPs and giant SEPs conditions. This is most likely due to the fact that Fz, the reference electrode on the SSEPs condition, is influenced by cortical SEPs [12, 13]. In addition, a previous report described that the amplitude of the middle latency cortical component after N20 decreases with use of a high bandpass filter and high stimulus rate [11, 14].

In this study, the N20−P25 amplitude on SSEPs was equivalent to 78% of that on giant SEPs. The initial prototype of recording condition of giant SEPs was described in 1977, which used a logarithmic scale and considered deviation beyond 2.38SD from the mean value of the normal control group as abnormal [2]. Based on the data, the same group determined an SEP as 'giant' when N20−P25 amplitude was larger than 8.6 μV or P25−N33 amplitude was larger than 8.4 μV [2, 3]. In 1990's, the upper normal limit was set

at the mean + 3SD of the logarithmic values recorded from normal subjects, i.e., N20−P25 amplitude larger than 6.3 µV and P25−N35 amplitude larger than 9.8 µV [5, 6](Ikeda et al., 1995; Terada et al., 1997). More recently, the mean + 3 SD of amplitudes obtained from the control subjects without logarithmic transformation are employed; N20−P25 >10.0 µV or P25−N35 >8.1 µV for the younger subgroup and N20−P25 >20.0 µV or P25−N35 >14.8 µV for the older subgroup [8]. In general, it is currently accepted that an amplitude more than 10 µV have high diagnostic significance in cortical myoclonus and epilepsy [9]. Our findings suggest that N20−P25 amplitude larger than 8 µV in the SSEP condition could be considered as giant SEPs. In the posterior tibial nerve stimulation, the upper limit was set at the mean + 2SD [4] or +3SD [7] of normal subjects. We previously evaluated a diagnostic validity of giant evoked potentials using different upper limits, i.e., the mean + 2SD or the mean +3SD, in familial myoclonic epilepsy [11]. Cumulative data would enable us to determine the optimum reference range in accordance with the purpose of evaluation and the tentative diagnosis.

The increased amplitude of SEPs can be seen in patients with other central nervous system disorders, such as cerebrovascular disease, demyelinating disease, spinal cord disease, and hydrocephalus [15]. Thus, it can be useful in patients with suspected central nervous system pathologies. In patients with amyotrophic lateral sclerosis, a report showed that an SEP amplitude of more than 8 µV on SSEPs is a predictive factor for poor prognosis [16]. The amplitude corresponds to 10 µV for the giant SEPs, as shown in our study. Abnormal enhancement of cortical excitability can be associated with worsening of neurodegeneration, and evoked potential amplitude can be a surrogate marker for disease progression. A recent study of conventional SEPs recording which set the upper limit at the mean + 2.5 SD, giant SEPs were found in 6.6% of patients evaluated in neurology department [17]. It should be emphasized that a tentative diagnosis of functional disorders would need to be reconsidered if amplitude of SEPs were enlarged.

The most important limitation of this study is small sample size. However, in previous studies control data were determined from approximately 20 normal subjects [2, 5, 8]. Large studies across a wide range of age groups would be useful to confirm the correlation between the two conditions.

In conclusion, our study showed that the amplitude in SSEPs condition was equivalent to approximately 80% of that in the giant SEPs condition. Further studies, including various neurological disorders, are warranted to evaluate the diagnostic significance and the predictive value for prognosis.

Declarations

Data availability

Anonymized data not published within this article will be made available upon request.

Author contributions

A.D. contributed conception and design of the study, acquisition and analysis of data, and drafted the manuscript. Y.D. contributed acquisition and analysis of data. K.S. critically reviewed the manuscript and prepared the figures. M.K. contributed conception and design of the study, acquisition and analysis of data, and revised the manuscript and figures.

Competing interests

The authors declare no competing interests.

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Figures

Fig 1

		SSEPs	Giant SEPs
Reference electrode	:	Fz	The earlobe electrode ipsilateral to the stimulated limb
Bandpass filter	:	20 Hz–3 kHz	1 Hz–1 kHz
Analysis times	:	100 msec	200 msec
Average number	:	300–500 stim	50–100 stim
Stimulus rate	:	5 Hz	1 Hz

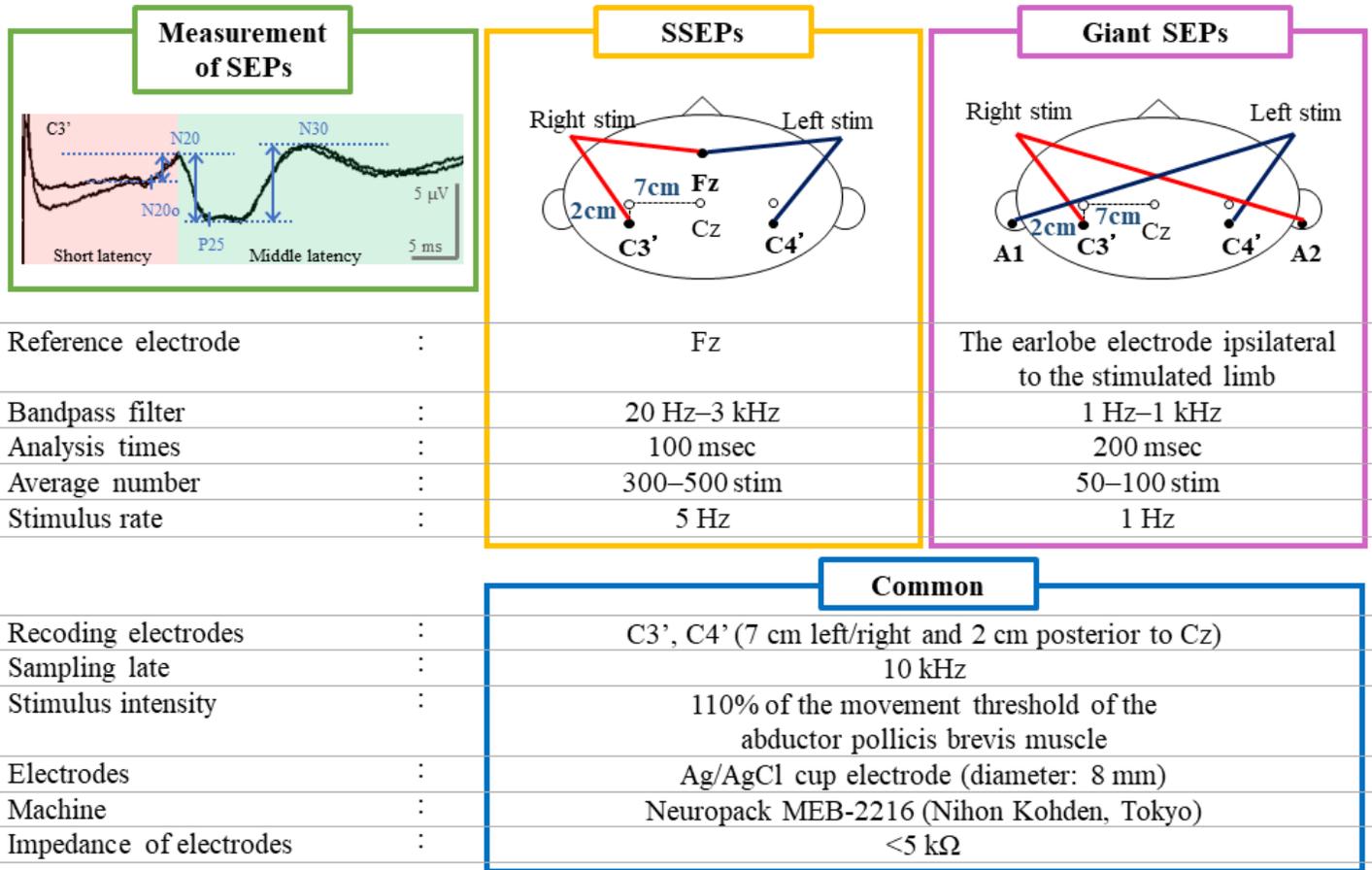|		Common	
Recoding electrodes	:	C3', C4' (7 cm left/right and 2 cm posterior to Cz)	
Sampling late	:	10 kHz	
Stimulus intensity	:	110% of the movement threshold of the abductor pollicis brevis muscle	
Electrodes	:	Ag/AgCl cup electrode (diameter: 8 mm)	
Machine	:	Neuropack MEB-2216 (Nihon Kohden, Tokyo)	
Impedance of electrodes	:	<5 kΩ	

Figure 1

Comparison of recording condition. Green box: amplitude measurement of somatosensory evoked potentials (SEPs). Recording conditions differ between short-latency SEPs (SSEPs) (yellow box) and giant SEPs (pink box). Blue box: Recording conditions common to both SEPs.
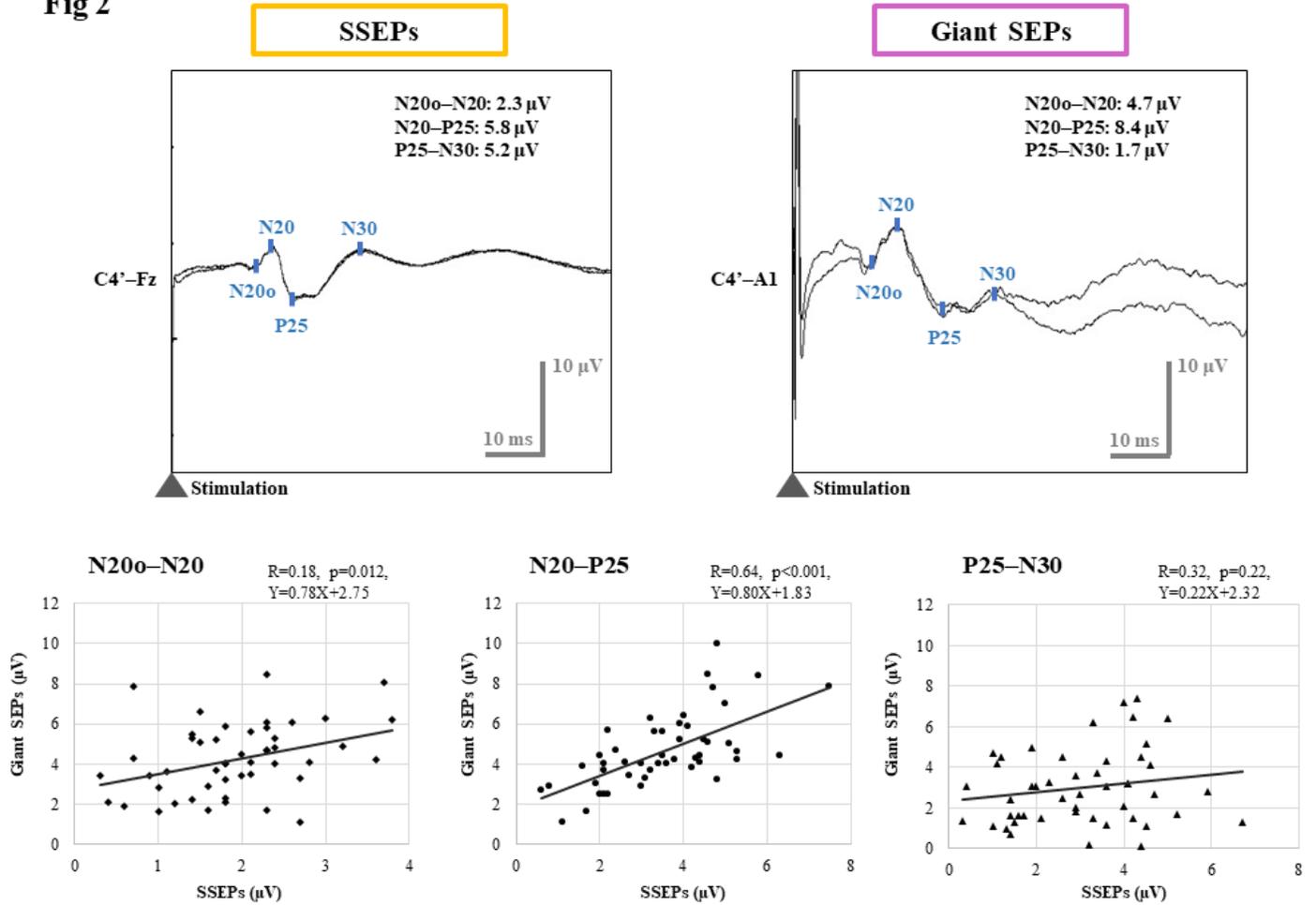
Figure 2

Comparison of amplitude between recording conditions. Upper row: Representative waveforms of a 23-year-old female, recorded by stimulating the left median nerve at the wrist. The amplitudes of N20o−N20 and N20−P25 are larger on the giant somatosensory evoked potentials (SEPs) condition than on the short-latency SEPs (SSEPs) condition. Lower row: Scatter plots of the giant SEPs amplitudes (ordinate) against the SSEPs amplitudes (abscissa), showing significant linear correlation of N20−P25 amplitude. Significance was confirmed by using Spearman's rank correlation (ρ=0.666, p<0.001).
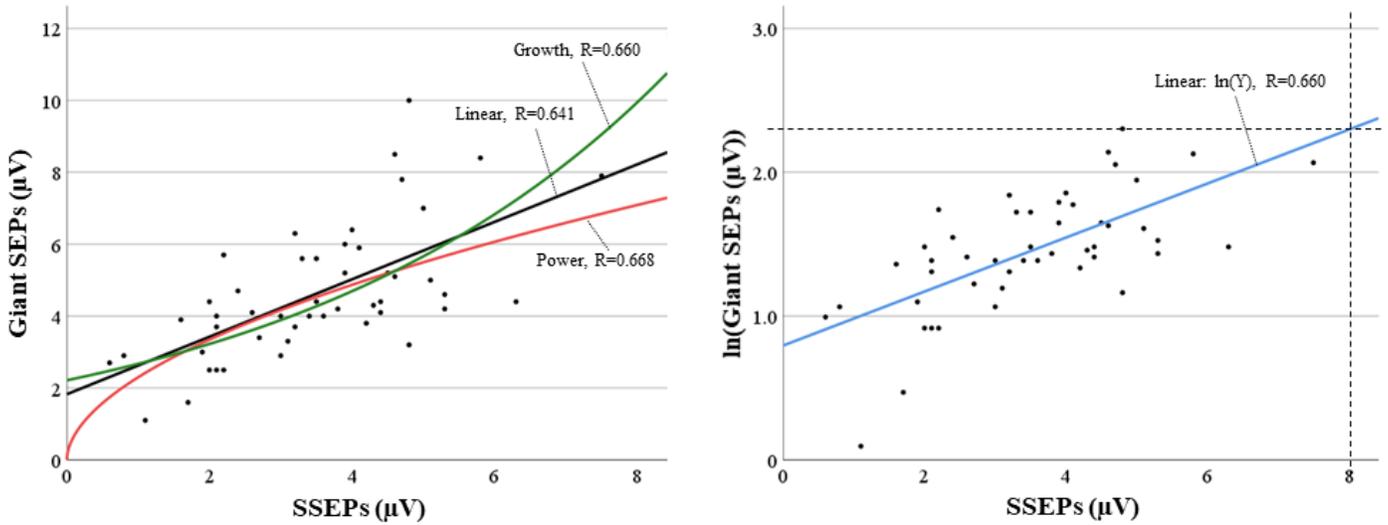
Fig 3

Figure 3

Correlation analysis of amplitude between recording conditions. Scatter plots of the giant somatosensory evoked potentials (SEPs) N20−P25 amplitude (ordinate) against the short-latency SEPs (SSEPs) amplitude (abscissa). Left: Curve-fit analysis, showing that growth (green) and power (red) models are more suitable than linear model (black). Right: Natural logarithmic transformation of giant SEPs amplitude (ordinate). According to linear model (blue), 10 μV on giant SEPs condition, i.e., ln(10) = 2.3, is equivalent to 8.0 μV on SSEPs condition (dotted lines).