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Appraisal of definition of baseline length for somatosensory evoked magnetic fields

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Highlights (maximum 85 characters)

- Stimulus onset should not be used for baseline segment in estimating dipoles
  (78 characters)
- Mean value of prestimulus periods could be used for analysis of evoked activities
  (83 characters)
- Mean value of whole raw data is available as baseline segment for evoked activities
  (85 characters)

Abstract

Background: The baseline (BL) segment in the prestimulus period is generally assigned as a reference of evoked activities. However, an experimenter empirically defines its length in each condition. So far, the criterion for the length of a BL segment has not been established.

New Method: We evaluated the effect of the length of the BL segment by recording somatosensory evoked magnetic fields (SEFs) under fixed stimulus onset asynchrony (SOA). For the evaluation of the length of the BL segment in the prestimulus period, five proportions in relation to SOA were used as the BL segment. In addition, we adopted other two types of BL segment which were the single data point measured from the value of stimulus onset (BL0) and the mean value of the whole raw data throughout the recording (DC mean). We investigated the influence of the BL segments on SEFs by utilizing two indicators: normalized N20m amplitudes and estimated locations of corresponding equivalent current dipoles (ECDs).

Results: Both indicators did not show any significant differences, based on the factor of BL segments, in any SOA conditions.

Comparison with Existing Method: The BL0 had by far the largest variation in the ECD locations.Therefore, utilizing stimulus onset as the BL segment should be avoided. In addition, considering that other BL segments provided comparable values by the two indicators, the DC mean can reasonably be adopted.

Conclusions: We suggest that utilizing the DC mean could be employed as the

BL segment.

Keywords

Magnetoencephalography (MEG); somatosensory evoked magnetic fields (SEF); Baseline segment

1. Introduction

The elevation at the top of a mountain is the height above the sea level. The sea level changes, based on the rise and fall of the tide; therefore, the height of a mountain is ostensibly different. To counteract this problem, the sea level is defined by taking the time-average of a near-by bay in Japan (The Geospatial Information Authority of Japan, accessed 2019, November 11). On a geographical basis, the average value is usually obtained across time in years. As with the height of a mountain, noninvasive investigations likewise utilize the time-average of amplitudes for the reference. However, owing to recording time limitations in electrophysiological recording methods, such as evoked responses and continuous recordings measured with electroencephalography or magnetoencephalography (MEG), the amplitudes of stimulus-related components are measured using one of three methods: (1) the peak height, based on only one point such as the stimulus onset (i.e., time zero); (2) the peak height from the preceding peak; or (3) the peak height from the baseline (BL) segment in the prestimulus period (Regan, 1989). However, amplitude measurement difficulties exist.

The timing of the reference taken in the first measurement method is farthest from the preceding stimulus. Therefore, this reference is least affected from responses produced by a preceding stimulus, including artifacts. However, this method assumes that the noise component at time zero will be effectively suppressed by increasing the number of averages, keeping the signal component of evoked responses constant. Therefore, using the stimulus onset as the reference may not be appropriate when averaging does not achieve sufficient numbers. The second measurement method could be adopted for the second and later components. However, this measurement could not be utilized for the first component because no preceding component exists before the first component for comparison. To counteract these problems (i.e., to minimize the noise component, including slower components), the average of the BL segments is employed for reference, starting backward in the prestimulus period from the stimulus onset. This reference method assumes that the activity in the BL segment is least affected by a preceding stimulus event in a similar manner to that at time zero. However, as the prestimulus BL lengthens, the risk of being affected by the preceding stimulus increases. Regarding this aspect, there are some variations of BL lengths across previous studies regarding how long a stimulus-related response persists after the preceding stimulus and how long backward we can employ the prestimulus proportion. Further, no particular criteria or guidelines exist for the length of the BL segment with regard to evoked responses. It appears that previous studies arbitrarily defined these parameters.

Previous reports utilized various BL lengths for this amplitude measurement (Table 1). The variety of BL lengths must be derived from different stimulus modalities, stimulus onset asynchronies (SOAs) or interstimulus intervals (ISIs), averaging times, and averaging time windows. For instance, in the amplitude measurement of somatosensory evoked potentials or somatosensory-evoked magnetic fields (SEFs), the stimulus onset or prestimulus period starting from 50 ms or 100 ms has been used as the reference (Araki et al., 1999; Babiloni et al., 2001; Egawa et al., 2008; Gatica Tossi et al., 2013; Hoshiyama et al., 1997; Nagamine et al., 1998). For auditory evoked potentials or auditory evoked magnetic fields, the prestimulus period of the BL segment is set to approximately 100 ms (Ohtomo et al., 1998; Takeshita et al., 2002). For visual evoked potentials or visual evoked magnetic fields, a prestimulus period of 50 ms or 100 ms was also used for the BL segment (Guthoff et al., 2011; Suzuki et al., 2015; Tobimatsu and Kato, 1996; Tsuruhara et al., 2013). However, no established criterion for the length of BL segment exists. In general, the BL segment is empirically defined by an experimenter.

The entire time of the averaging window has also been utilized for the BL segment in steady state responses (Gerloff et al., 1998a; Gerloff et al., 1997; Gerloff et al., 1998b). This whole-time assignment in the averaging time window is equivalent to employing 100% of the prestimulus period in case of steady state responses. The ultimate backward extension of the BL segment up to the immediately preceding stimulus inevitably includes evoked responses. This presumes that the component of evoked responses becomes zero by averaging along the time axis. If this assumption holds true, then employing the entire raw data as the BL may also be applicable, assuming that the trials with responses and artifacts are also regarded as having a zero average.

In the present study, we appraised the length of the BL segment to determine the appropriate length to use for analyzing evoked responses. We also investigated the influence of the BL segment by using the first component of somatosensory evoked responses as samples.

2. Methods

2.1. Study participants

Six right-handed healthy men participated in this study. They had a mean age (presented as the number ± standard deviation) of 28.2 ± 8.0 years and had no history of neurological, psychiatric, sensory, or movement disorder. The study was approved by the ethics committee of Sapporo Medical University (Sapporo, Japan). We obtained written informed consent from each participant before the experiment.

2.2. Sample data

2.2.1. Stimulation

Each participant lay supine on the scanner bed inside a magnetically shielded room. They were requested to relax with their eyes open and to avoid frequent blinking throughout the recordings.

For the electrical stimulation, the right median nerve was stimulated at the wrist with the 0.2-ms constant current pulses delivered through a pair of electrodes. The stimulus intensity was adjusted to evoke a thumb twitch at 10% above the motor threshold.

2.2.2. Stimulus onset asynchrony

Three types of fixed SOAs were employed: 4 s, 2 s, and 0.5 s. The participants were stimulated approximately 150 times in a session. In addition, two sessions were successively conducted for each SOA. The order of the three different SOAs was counterbalanced among the participants. Short breaks were introduced between the two sessions and between the three SOA conditions. Therefore, six sessions of recording were conducted, and the total recording time was approximately 1 h.

2.2.3. Magnetoencephalography recordings

Magnetoencephalographic data were recorded by using a whole-head 204-channel planar gradiometer with a superconducting quantum interference device (Elekta Neuromag Vectorview, Helsinki, Finland). Magnetoencephalography uses two orthogonal eight-shaped pickup coils at 102 measuring sites.

Along with the MEG data, the vertical electro-oculogram (EOG) and surface electromyogram (EMG) for the right thenar muscle were monitored to check the recording condition. The recording passbands were 0.10–300 Hz for MEG, 0.53–120 Hz for EOG, and 5.3–300 Hz for EMG. The continuous data were sampled at 1012 Hz. Furthermore, four head position indicator (HPI) coils were attached to the skin of the forehead and behind the ears. The three-dimensional (3-D) coordination of the HPI coils and three anatomical fiducial points (i.e., the nasion and bilateral preauricular points) was digitized for the coregistration of the MEG data (Hamalainen, 1993). Three-dimensional T1-weighted magnetic resonance images (MRIs) (200 slices, voxel size = 1 mm × 1 mm × 1 mm) were acquired with a 3.0-Tesla scanner (Signa; GE Healthcare, Chicago, IL, USA).

2.2.4. On-line evoked responses

We evaluated the on-line averages to secure firm responses such that our main analysis by using an off-line method would have adequate data of a certain length. We averaged the responses with a time window of -50 ms to 500 ms, and excluded trials having an EOG reading exceeding 150 μV. We stopped averaging the on-line evoked responses when the number of averages reached 150, and again, replicated the trial to confirm the first evoked response of approximately 20 ms. We also recorded continuous data from the beginning.

2.2.5. Off-line data processing

Acquired continuous MEG data were first preprocessed to exclude noises originating from inside and outside the sensor array by using tSSS (MaxFilter™ V2.1.15; Elekta Neuromag, Helsinki, Finland) in an off-line method. The averaging time window started from the time preceding the stimuli and ended at the following stimuli, having the target trigger stimuli as the middle stimulus (Figure 1). As a result, the averaging time windows were -4000 to 4000 ms, -2000 to 2000 ms, and -500 to 500 ms for the 4-s, 2-s, and 0.5-s SOA conditions, respectively. The off-line evoked responses were tentatively obtained by averaging the epochs of the preprocessed data with the averaging time window, after excluding epochs contaminated with artifacts due to eye blinks or other sources (larger than 150 μV peak to peak by EOG). Thereafter, the final averages were obtained by sharing the minimum number of artifact-free epochs across sessions and study participants.

2.3. Baseline

We adopted three types of BL segments for the amplitude measurement. The first BL type was the mean value of predetermined prestimulus periods (Figure 1). We defined the periods, based on the proportion with respect to the SOA: 5%, 10%, 20%, 50%, and 100% for the BL5, BL10, BL20, BL50, and BL100 assignments, respectively. The second BL type was the measurement of the amplitude from the level at the value of the stimulus onset (i.e., BL0 assignment). It used the single data point alone for the stimulus onset. For the third BL type, the mean value of the whole raw data was utilized as the BL segment (termed the "DC mean assignment").

2.4. Two evaluation indicators

We introduced two factors to evaluate the effect of BL assignments: (1) the N20m amplitude measured at a single sensor showing a maximal response and (2) the location of single ECDs estimated from multiple sensors (Fig. 2).

2.4.1 Selection of a target sensor

For each participant, we determined one target sensor from among 204 sensors in the 4-s SOA condition that showed the largest 4-s time-average response.

2.4.2. Normalized N20m amplitude

The N20m amplitude of the target sensor in each condition was measured at the peak from the level of each BL segment defined in the "*2.3. Baseline*" section (Fig. 3A). The amplitudes of N20m were normalized to the amplitudes measured in the 4-s SOA condition with the BL0 assignment to minimize interindividual variations in the response amplitude.

2.4.3. Source localization for the N20m component

Single ECD analysis of the N20m latency was conducted by using a spherical head model. The 3-D coordinates of ECDs were acquired from 18 channels of a planar gradiometer that included a channel showing the local maximal response of the primary somatosensory area and N20m latency (Fig. 3B). These channels selected and latencies for N20m localization were fixed in each subject irrespective of the type of SOAs or BL segments. The consequent estimated sources were superimposed onto a participant's own MRI image. To select reliable sources alone, we accepted ECDs only when they fulfilled the criteria of a goodness-of-fit value > 80% and a confidence volume < 2000 mm^3.

With regard to the effect of BL assignment and/or SOA condition on ECD location, we introduced two types of reference ECDs and calculated the distance from the two reference ECDs to the ECD locations (Fig. 4). For the first, we set up a new ECD with the coordinate position averages of ECDs with different BL assignments for each SOA condition separately (ECDm) as a within-group reference (Fig. 4A). For the second, we adopted the ECD obtained by the BL0 assignment in the 4-s SOA condition ($ECD_{BL0\text{-}4s}$) as the overall common reference (Fig. 4B). The distances were measured from two reference ECDs to each ECD; further, the mean distance from ECDm was described as the "VAR_{ECDm}[BL assignment, *]" or as [*, SOA condition], and that from $ECD_{BL0\text{-}4s}$ was indicated as the "$VAR_{BL0\text{-}4s}$[BL assignment, *]" or as [*, SOA condition].

The asterisk (*) indicates “across the BL assignment” or “across the SOA condition” (e.g. “VAR_{ECDm}[*, 4]” indicates the mean distance from ECDm to each ECD in 4-s SOA condition).

2.5. Statistical analyses

The normalized N20m amplitudes were compared across seven BL assignments and three SOA conditions using the Friedman test. If the Friedman test showed a significant difference, the Wilcoxon signed rank test with Bonferroni correction was utilized between BL assignments and/or SOA conditions as the *post-hoc* test. A significant P-value was < 0.05. For the source localization, VAR_{ECDm} and $VAR_{BL0\text{-}4s}$ were evaluated similarly across the seven BL assignments and/or three SOA conditions by using the Friedman test and Wilcoxon signed rank test with Bonferroni correction, using statistical analysis software (IBM SPSS Statistics, version 24; IBM).

3. Results

3.1. Single sensor analysis of the normalized N20m amplitudes

We confirmed that the evoked responses in the two sessions had a similar configuration and peak latencies for N20m in each SOA condition in all study participants. Therefore, we primarily analyzed the evoked responses by averaging the two sessions. In total, the averaging number was 160 in each SOA condition, which was derived from the minimum number of artifact-free epochs across sessions and study participants. The N20m was confirmed around 20 ms in all subjects, regardless of the SOA condition (Fig. 5A). The mean normalized N20m amplitudes were 97.5%, 89.7% and 91.1% in the 4-s, 2-s, and 0.5-s SOA conditions, respectively (Fig. 6 and Table 2). The normalized N20m amplitudes in terms of the BL assignments revealed a significant difference, based on the Friedman test, for the 2-s ($P = 0.004$) SOA condition. However, further analysis using the Wilcoxon signed rank test did not show any significant difference among the BL assignments ($P > 0.05$). On the other hand, the comparison revealed a significant difference among SOA conditions ($P = 0.003$). *Post-hoc* analysis showed significant differences between the 4-s and 2-s SOA conditions ($P < 0.001$) and between the 4-s and 0.5-s SOA conditions ($P = 0.009$). Therefore, in this experiment, the 4-s SOA condition had a larger N20m amplitude than did the 2-s and 0.5-s SOA conditions (Fig. 6 and Table 2).

3.2. Multisensor analysis of N20m

We estimated the ECDs for N20m from the consolidated 160 averages in each SOA condition. The ECDs were located on the central sulcus around the "hand knob" area, regardless of the SOA condition (Fig. 5B). The estimated locations of all ECDs derived from the seven BL assignments in a representative individual (No. 1) are shown in Fig. 7 for each SOA condition. They were located over the primary somatosensory area in all SOA conditions. In this individual, we evaluated the variation in the ECD location from the two reference ECDs. The first reference of ECDm revealed $VAR_{ECDm}[*, 4] = 0.6 \pm$

0.5 mm, VAR_{ECDm}[*, 2] = 0.6 ± 0.4 mm, and VAR_{ECDm}[*, 0.5] = 0.8 ± 0.6 mm, and the second reference of ECD_{BL0-4s} showed VAR_{BL0-4s}[*, 4] = 1.5 ± 0.7 mm, VAR_{BL0-4s}[*, 2] = 1.7 ± 0.3 mm, and VAR_{BL0-4s}[*, 0.5] = 2.9 ± 0.7 mm.

We applied the variation in the ECD location by taking the ECDm (i.e., VAR_{ECDm}) for the group analysis of all study participants (Fig. 8A and Table 3). The Friedman test on VAR_{ECDm}s among BL assignments revealed a significant difference for the 4-s (P = 0.008) and 2-s (P = 0.031) SOA conditions. The following *post-hoc* test did not show any significant difference in any BL assignment (P > 0.05). However, the variation in the BL0 assignment was approximately twice as large as that of other BL assignments, including the DC mean assignment (Fig. 8A). Therefore, the largest VAR_{ECDm}[*, *] becomes 3.9 mm from 7.1 mm, if the BL0 assignment is excluded.

The VAR_{ECDm}s for SOA conditions revealed a significant difference (P < 0.001), and the subsequent *post-hoc* test revealed a significant difference between the 4-s and 0.5-s SOA conditions (P < 0.001) and the 2-s and 0.5-s SOA conditions (P = 0.030). The VAR_{ECDm} of the 0.5-s SOA condition was larger than that of the 4-s and the 2-s SOA conditions. Therefore, the BL assignment did not significantly affect VAR_{ECDm}s, whereas the SOA conditions did significantly influence the VAR_{ECDm}s. The 0.5-s SOA condition showed the largest VAR_{ECDm}s.

Similar to the VAR_{ECDm}s, we evaluated the variation in the ECD location by taking the ECD obtained on BL0 assignment in the 4-s SOA condition instead of the ECDm (i.e., VAR_{BL0-4s}) as the second reference of the ECD (Fig. 8B and Table 4). Among the BL assignments, the Friedman test on VAR_{BL0-4s}s revealed a significant difference in the 4-s SOA condition (P = 0.003). However, the *post-hoc* test did not show a significant difference in any BL assignment (P > 0.05). The $VAR_{BL0\text{-}4s}$s for the SOA conditions showed a significant difference (P < 0.001). In addition, the post-hoc test showed a significant difference between all combinations of SOA conditions: 4 s versus 2 s (P < 0.001), 4 s versus 0.5 s (P < 0.001), and 2 s versus 0.5 s (P = 0.039). Hence, the largest $VAR_{BL0\text{-}4s}$ was in the 0.5-s SOA condition, followed in order by the 2-s and 4-s SOA conditions. Therefore, the BL assignment did not affect $VAR_{BL0\text{-}4s}$s significantly, although the SOA conditions had a significant influence on $VAR_{BL0\text{-}4s}$.

4. Discussion

In the present study, we investigated the influence of the length of the BL segment on somatosensory evoked responses. We focused on N20m and evaluated it by two indicators: normalized amplitudes and estimated locations of ECDs. The normalized N20m amplitudes did not significantly differ in any SOA condition based on BL assignment. With regard to the locations of the estimated ECDs among seven BL assignments, we found no significant difference in any BL assignment. These findings indicated that an absolute index for the baseline segment cannot be determined. Therefore, we suggest that any BL assignment can be adopted for the amplitude measurement of N20m and for the ECD estimation.

In the present study, the SOA condition had a significant influence on the normalized N20m amplitude, whereas the BL assignment did not. A noteworthy finding was that the number of time points digitized in the BL assignments was also affected by the proportion of the SOA. This relationship indicated that the number of averaging across trials may matter, as does the BL assignment, because it influences the signal-to-noise ratio at each time point.

Among the invasive technique for functional brain-mapping, electrocorticography (ECoG) is widely utilized either by cortical stimulation or detection of evoked responses, and can discriminate between task-related areas (Hill et al., 2012) or several motor-related areas (Miller et al., 2007). Although most ECoGs use an interelectrode distance of 10 mm in a clinical recording, some adopt a 5 mm interelectrode distance (Boran et al., 2019; Hill et al., 2012; Miller et al., 2007). Therefore, the functional spatial resolution of ECoG can be considered to be 5 mm. In addition to the invasive technique, MEG is widely utilized as a noninvasive technique, and previous literature reports showed that the error of ECD estimation ranged from 4 to 10 mm (Cohen et al., 1990; Virtanen et al., 1998). In our study, the VAR_{ECDm} was smaller than 10 mm in any BL segment or any study participant in all SOA conditions, and all ECDs across all study participants were within the 10-mm radius sphere around the left postcentral gyrus, regardless of SOA condition or BL segment length. However, among the seven BL assignments, the BL0 yielded exceptionally different results. If the BL0 assignment is excluded, the largest VAR_{ECDm}[*, *] becomes 3.9 mm from 7.1 mm. This smaller variation by the exclusion of BL0 better matches the minimum spatial resolution of 4 mm derived from previous functional spatial resolution of ECD (Virtanen et al., 1998). Thus, the BL0 assignment should be avoided for measuring the ECD location.

Among the three types of BL assignments, the first BL type (i.e., the mean of predetermined prestimulus period) is generally utilized for BL segments. This type of BL assignment can adopt even one cycle of the SOA or ISI at most in this experiment of fixed SOAs. However, the DC mean assignment, (i.e., the third BL type), had a longer duration for the calculation of the mean value, including epochs contaminated with artifacts due to eye blinks or other sources. Thus, the influence of artifacts is minimized after being averaged with a long duration data. This conceptual inference is supported by our data showing that the BL assignment, including the DC mean, did not affect the indicators. Therefore, the DC mean can be employed as a BL segment as in other conventional BL settings. In addition, the DC mean employs the whole raw data; therefore, the fluctuation of SOA and ISI can be utilized.

We checked the SEFs only after the median nerve stimulation; therefore, we cannot refer directly to the influences of BL segments versus those evoked by other stimulus modalities. Evoked responses depend largely on the sensory modality. The modalities have different time-scale responses; thus, the effect of a BL segment must be verified in each modality. However, we defined the BL segments, based on the proportion before the stimulus onset with respect to the fixed SOAs. Therefore, our results may be applied to responses in other stimulus modalities. In addition, since we utilized the fixed SOAs for the analysis object, we could not discuss the effect of the randomized SOAs or ISIs in the current study. Although randomized SOAs or ISIs are widely utilized to avoid the synchronization of artifacts in clinical recordings of evoked responses, we did not include it as a parameter for the sample recordings because we needed to control the variation width in addition to the interval itself. However, we adopted the averaging technique, where the effect of randomized variation is estimated to be minimal compared with the effect of BL assignments. In addition, we could not investigate the filter effect, especially for the high-pass filter that had the effect of a slower component. Moreover, evoked responses are influenced by several conditions, including task, attention, and/or intensity of stimulations. Therefore, these factors need to be examined in future studies.

In the current study, we investigated the three types of BL segments and found that the second BL type of assignment (i.e., BL0) was unreliable. Our new BL setting of the DC mean using whole raw data revealed justified results that were comparable to other BL settings. Thus, the entirety of the data can be utilized as the baseline.

5. Conclusion

In this study, we investigated the influence of the length of the BL segment on the SEF and found no significant differences among the seven BL assignments in N20m amplitude and ECD locations. However, the BL segment of stimulus onset had the largest variation in the ECDs. Therefore, utilizing stimulus onset as the BL segment should be avoided. In addition, as the DC mean employs the whole raw data, the regularity of stimuli expressed by SOA or ISI is not an important factor. Thus, utilizing the DC mean could be employed as the BL segment.

Declarations of interest:

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Tables

Table 1

Studies investigating evoked responses with various modalities

Authors (year)	Modality	SOA or ISI (ms)	Averaging times	BL segment (ms)
Hoshiyama (1997)	SEF	1,000	400	-100 ~ 0
Nagamine (1998)	SEP and SEF	900 and 4,000	200	-100 ~ -5
Ohtomo (1998)	SEF	370	200	-20 ~ 0
	AEF	2,500 ~ 4,700	50	-100 ~ 0
Babiloni (2001)	SEP	330	600	-50 ~ 0
Torquati (2002)	SEF	3,300	120	+10 ~ +15
Egawa (2008)	SEF	350 ~ 380	300	-50 ~ 0
Takeshita (2002)	AEP and AEF	1,600, 3,000 and 5,000	100	-100 ~ 0
Guthoff (2011)	VEF	2,500	45	-100 ~ 0
Tsuruhara (2013)	VEF	500	180	-50 ~ 0
Suzuki (2015)	VEF	500	100	-100 ~ 0
Gerloff (1998)	MRCF	500	1,000	-300 ~ +200

SEF: somatosensory evoked magnetic fields, SEP: somatosensory evoked potential, AEF: auditory evoked magnetic field, AEP: auditory evoked potential, VEF: visual evoked magnetic field, MRCF: movement related cortical magnetic field

Table 2

The N20m amplitudes normalized to amplitudes measured from the stimulus onset in the 4-s stimulus onset asynchrony condition

	SOA = 4 s	SOA = 2 s	SOA = 0.5 s
BL5	95.0 (8.5)	88.5 (9.0)	90.4 (28.1)
BL10	93.9 (6.9)	89.2 (9.1)	88.4 (31.0)
BL20	94.7 (9.5)	88.7 (5.7)	89.2 (26.9)
BL50	98.2 (11.5)	88.5 (4.1)	85.0 (25.6)
BL100	99.6 (12.1)	93.0 (6.4)	97.9 (25.9)
BL0	100.0 (0.0)	85.7 (11.9)	88.1 (26.5)
DC mean	100.7 (14.7)	94.5 (5.8)	98.6 (29.0)
Mean	97.5 (*1, *2)	89.7 (*1)	91.1 (*2)

The values are presented as percentages of the normalized N20m amplitudes as the medians and interquartile ranges for all study participants (%). “Mean” indicates the averaged value of the medians of each baseline (BL) assignment and stimulus onset asynchrony (SOA) condition. The normalized N20m amplitude differs significantly between the 4-s and 2-s SOA conditions (*1: $P < 0.001$) and between the 4-s and 0.5-s SOA conditions (*2: $P = 0.009$).

Table 3

The variation in the equivalent current dipole location, measured from the mean equivalent current dipole across the seven types of baseline assignments and the stimulus onset asynchrony conditions (VAR_{ECDm})

	SOA = 4 sec	SOA = 2 sec	SOA = 0.5 sec
BL5	0.5 (0.3)	0.9 (0.6)	1.1 (0.8)
BL10	0.5 (0.4)	0.8 (0.8)	0.9 (0.7)
BL20	0.4 (0.4)	0.6 (0.9)	1.2 (1.3)
BL50	0.6 (0.6)	0.6 (0.5)	1.3 (0.8)
BL100	0.8 (0.6)	1.0 (0.6)	1.1 (0.9)
BL0	1.8 (0.8)	1.9 (1.3)	2.4 (3.2)
DC mean	1.1 (0.8)	1.0 (0.4)	1.3 (1.3)
Mean	0.8 (*1)	1.0 (*2)	1.4 (*1, *2)

The values are presented as medians, followed by interquartile ranges in parentheses, all in mm unit. “Mean” indicates the average value of the medians of each BL assignment and SOA conditions. The mean VAR_{ECDm} across BL assignments differs significantly between the 4-s and 0.5-s SOA conditions (*1:

P < 0.001) and between the 2-s and 0.5-s SOA conditions (*2: P = 0.030). ECD: equivalent current dipole, ECDm: mean ECD, VAR_{ECDm}: variation of ECD location (based on the mean distance of the ECD from the ECDm), BL: baseline, SOA: stimulus onset asynchrony

Table 4

The variation of equivalent current dipole (ECD) location using the ECD obtained from the BL0 assignment in the 4-s stimulus onset asynchrony (SOA) condition instead of the mean ECD across the seven types of baseline assignments and the SOA conditions (VAR_{BL0-4s})

	SOA = 4 sec	SOA = 2 sec	SOA = 0.5 sec
BL5	1.8 (0.9)	3.1 (1.4)	5.1 (3.6)
BL10	2.0 (0.3)	3.5 (1.9)	4.9 (4.6)
BL20	2.2 (0.8)	3.3 (1.9)	4.3 (6.2)
BL50	2.6 (1.2)	3.4 (2.4)	4.8 (5.9)
BL100	2.3 (1.5)	4.1 (2.3)	5.8 (5.2)
BL0	0.0 (0.0)	3.5 (3.3)	4.6 (5.5)
DC mean	2.7 (1.8)	4.2 (2.0)	6.2 (5.4)
Mean	1.9 (*1, *2)	3.6 (*1, *3)	5.1 (*2, *3)

The values are presented as medians, followed by interquartile ranges in parentheses, all in mm unit. “Mean” indicates the average value of the medians of each BL assignment and SOA condition. The mean VAR_{BL0-4s} across BL assignments differs significantly between the 4-s and 2-sSOA conditions (*1: P < 0.001), between the 4-sand 0.5-s SOA conditions (*2: P < 0.001), and between the 2-sand 0.5-s SOA conditions (*3: P = 0.039).

ECD: equivalent current dipole, BL: baseline, SOA: stimulus onset asynchrony, Var_{BL0-4s}, variation in the ECD location (based on the ECD obtained from the BL0 assignment in the 4-s SOA condition)

Figure legends

Figure 1

Five types of prestimulus baseline (BL) segments, defined as the first BL type. The proportion of the prestimulus period is defined with respect to stimulus onset asynchronies (SOAs). In this experiment in which the SOA is 4 s, the prestimulus 5%, 10%, 20%, 50%, and 100% correspond to 200 ms, 400 ms, 800 ms, 2000 ms, and 4000 ms, respectively. In addition, the second BL type was the level at the value of the stimulus onset (i.e., BL0 assignment). For the third BL type, the mean value of the whole raw data was utilized as the BL segment (termed the “DC mean assignment”). “Stim” indicates the timing of the stimulus onset. “Baseline periods” and “Evoked periods” indicate the prestimulus and poststimulus periods.

Fig. 2

The diagram depicts the evaluation of the effect of baseline (BL) assignments. Seven types of BL segments were adopted for single-sensor analysis and multisensor analysis of the three conditions of stimulus onset asynchronies. Single-sensor analysis contains the measurement of the maximum N20m amplitude from baseline to peak. The multisensor analysis includes the distance of equivalent current dipoles, based on seven types of BL segments.

Fig. 3

The method of amplitude measurement and dipole estimation of N20m. A: For the amplitude measurement of N20m, we selected the “from baseline to peak” method, and we could measure the first component of the evoked response. B: For the dipole estimation, we selected an 18-channel planar gradiometer. Single equivalent current dipoles were estimated at approximately 20 ms.

Fig. 4

Two types of reference utilized for the measurement of mean distance in a representative individual (No. 1): within-group reference (A) and overall common reference (B) in three stimulus onset asynchrony (SOA) conditions. A: Within-group reference; the distances from the equivalent current dipoles (ECDs) to the mean ECD (ECDm). The red dots; ECDm, the blue dots; seven ECDs of each baseline (BL) assignment. B: Overall common reference; the distance from the ECDs to the ECD obtained by the BL0 assignment in the 4-s SOA condition ($ECD_{BL0\text{-}4s}$). The red dots; $ECD_{BL0\text{-}4s}$, the blue dots; six ECDs of each BL assignment in the 4-s SOA condition and the seven ECDs of each BL assignment in the 2-s and 0.5-s SOA conditions.
Each coordinate value was shown in the corresponding reference.

Fig. 5

The waveforms of the somatosensory evoked magnetic field responses of all study participants, based on the channel recording the maximum N20m amplitudes of three stimulus onset asynchrony (SOA) conditions. The right median nerve was stimulated at the wrist. The maximum response was recorded from a sensor on the left hemisphere. The baseline (BL) was set on

BL0, and the time range was set from -10 ms to +50 ms. The red line indicates the 4-s SOA condition. The blue line indicates the 2-s SOA condition. The green line indicates the 0.5-s SOA condition.

Fig. 6

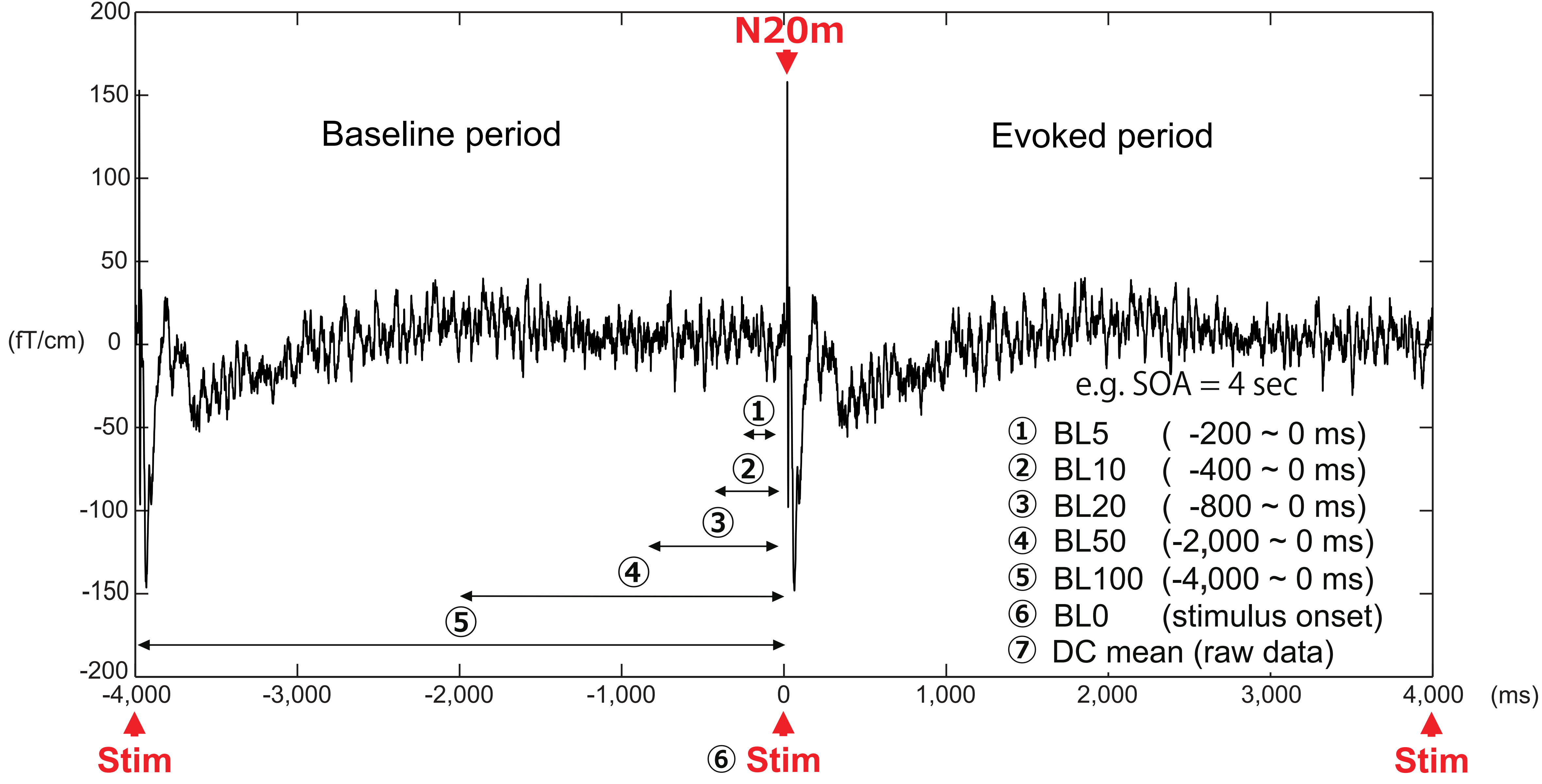
The box plots show the percentage of the normalized N20m amplitude as the median and interquartile range for all study participants.

Fig. 7

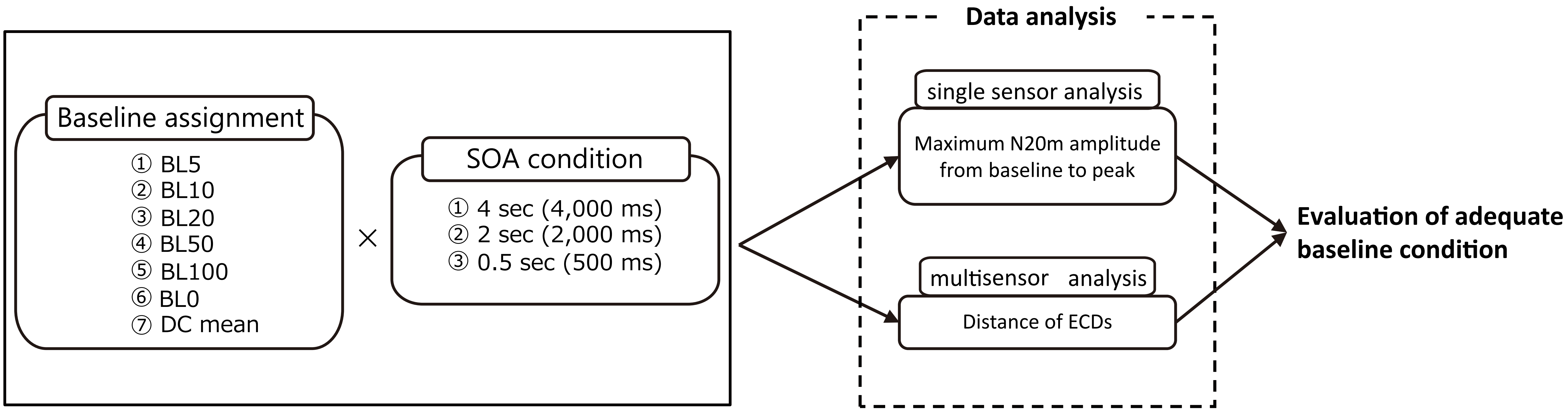
Evoked single equivalent current dipoles (ECDs) of seven baseline (BL) segments in a representative individual (No. 1). For all stimulus onset asynchrony conditions, all ECDs are included in a sphere with a radius of 10 mm. The blue line indicates BL5; the green line, BL10; the magenta line, BL20; the cyan line, BL50; the yellow line, BL100; the red line, BL0; and the white line, the DC mean (i.e., the mean value of whole raw data used for the BL segment).

Fig. 8

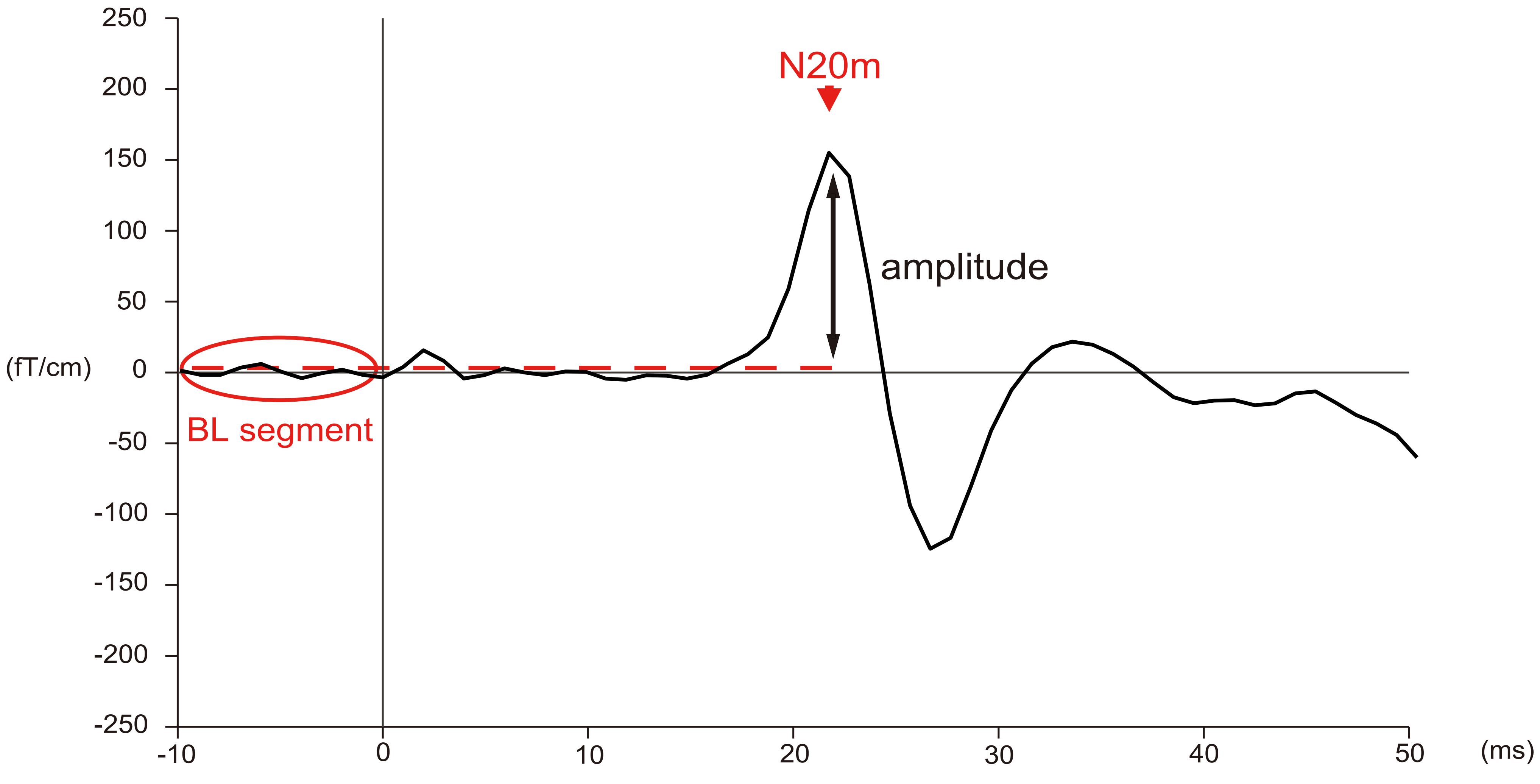
The box plots show the variation in the ECD location measured from the ECDm (VAR_{ECDm}) and the ECD obtained on BL0 assignment in the 4-s SOA condition ($Var_{BL0\text{-}4s}$) across the seven types of BL assignments and the SOA conditions. ECD: equivalent current dipole, ECDm: mean, BL: baseline, SOA: stimulus onset asynchrony.



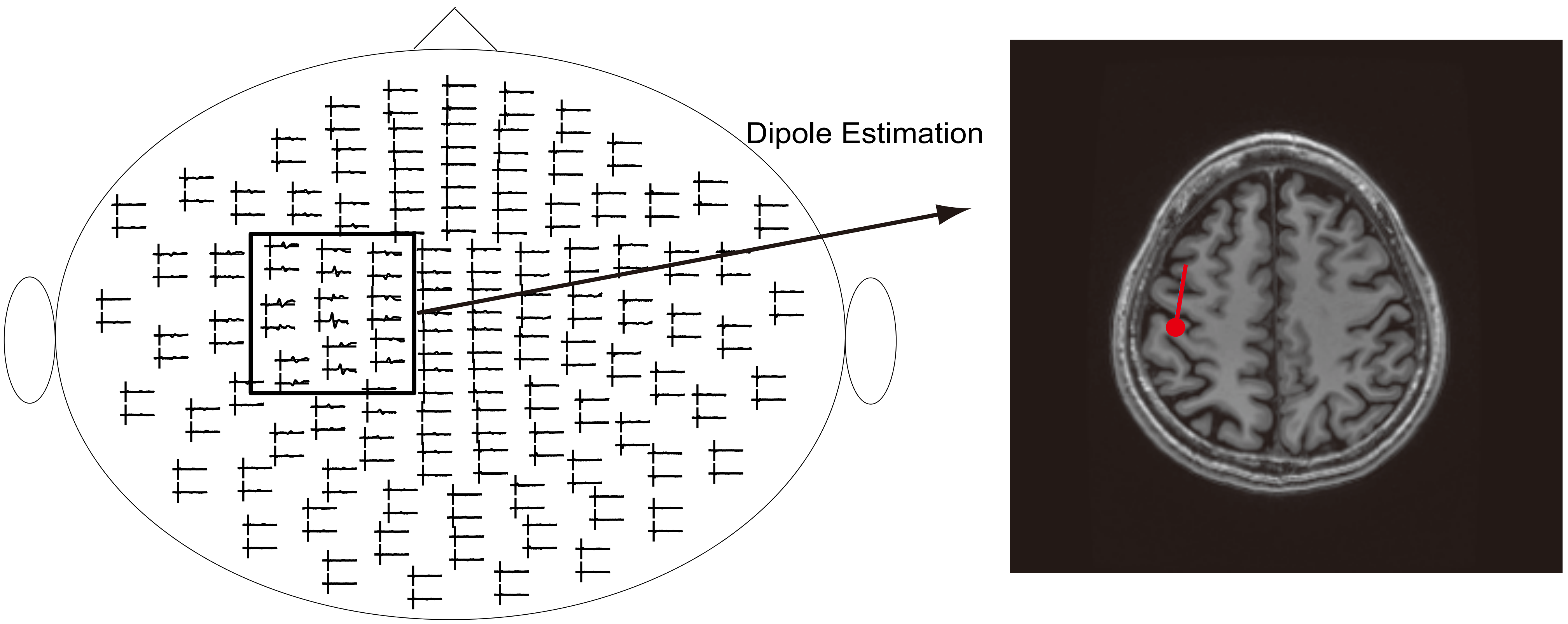
N20m
Baseline period
Evoked period
(fT/cm)
200
150
100
50
0
-50
-100
-150
-200
-4,000
-3,000
-2,000
-1,000
0
1,000
2,000
3,000
4,000
(ms)
e.g. SOA = 4 sec
① BL5 (-200 ~ 0 ms)
② BL10 (-400 ~ 0 ms)
③ BL20 (-800 ~ 0 ms)
④ BL50 (-2,000 ~ 0 ms)
⑤ BL100 (-4,000 ~ 0 ms)
⑥ BL0 (stimulus onset)
⑦ DC mean (raw data)
Stim
⑥ Stim
Stim

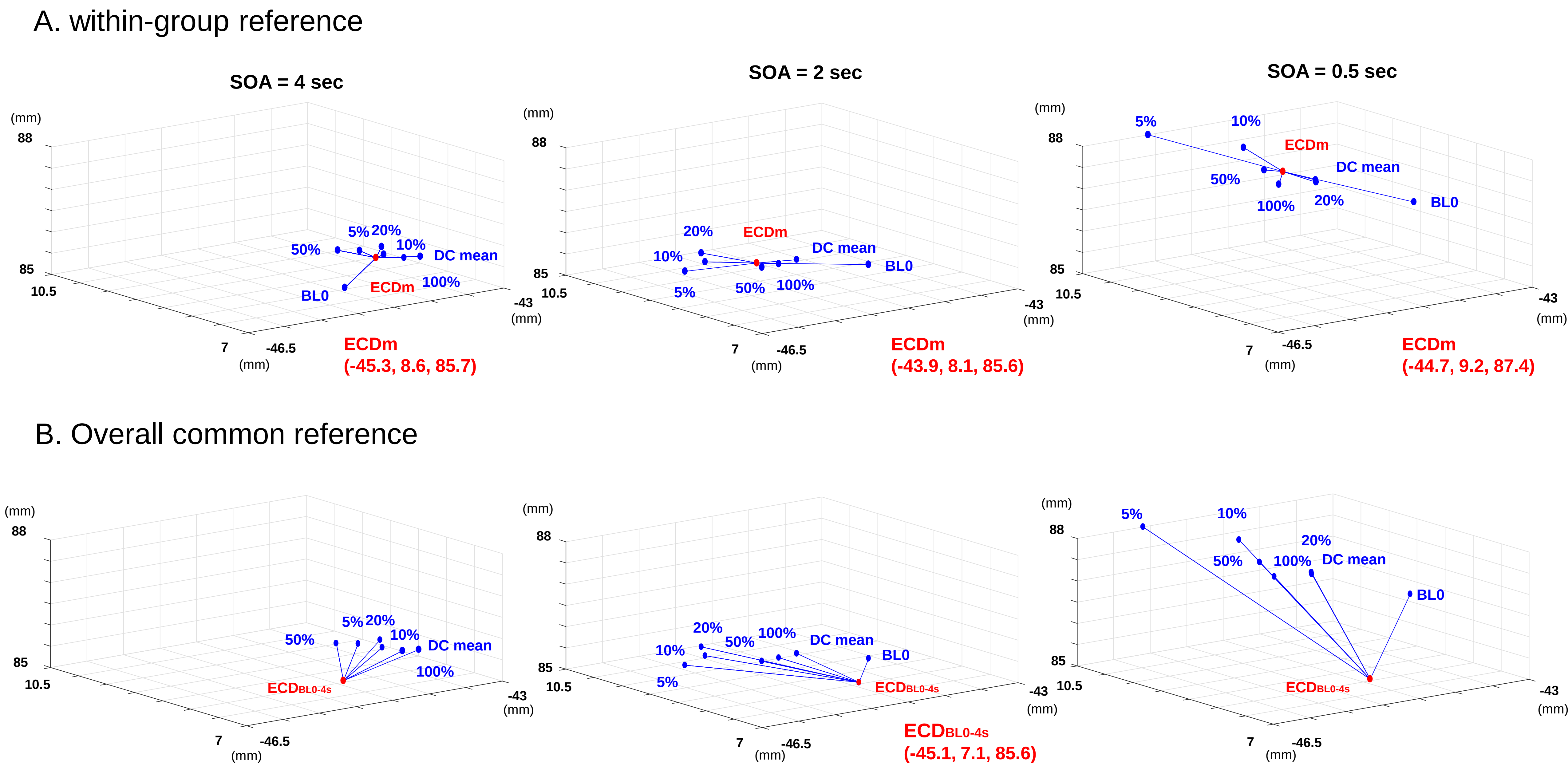

Baseline assignment
① BL5
② BL10
③ BL20
④ BL50
⑤ BL100
⑥ BL0
⑦ DC mean
×
SOA condition
① 4 sec (4,000 ms)
② 2 sec (2,000 ms)
③ 0.5 sec (500 ms)
Data analysis
single sensor analysis
Maximum N20m amplitude
from baseline to peak
multisensor analysis
Distance of ECDs
Evaluation of adequate
baseline condition

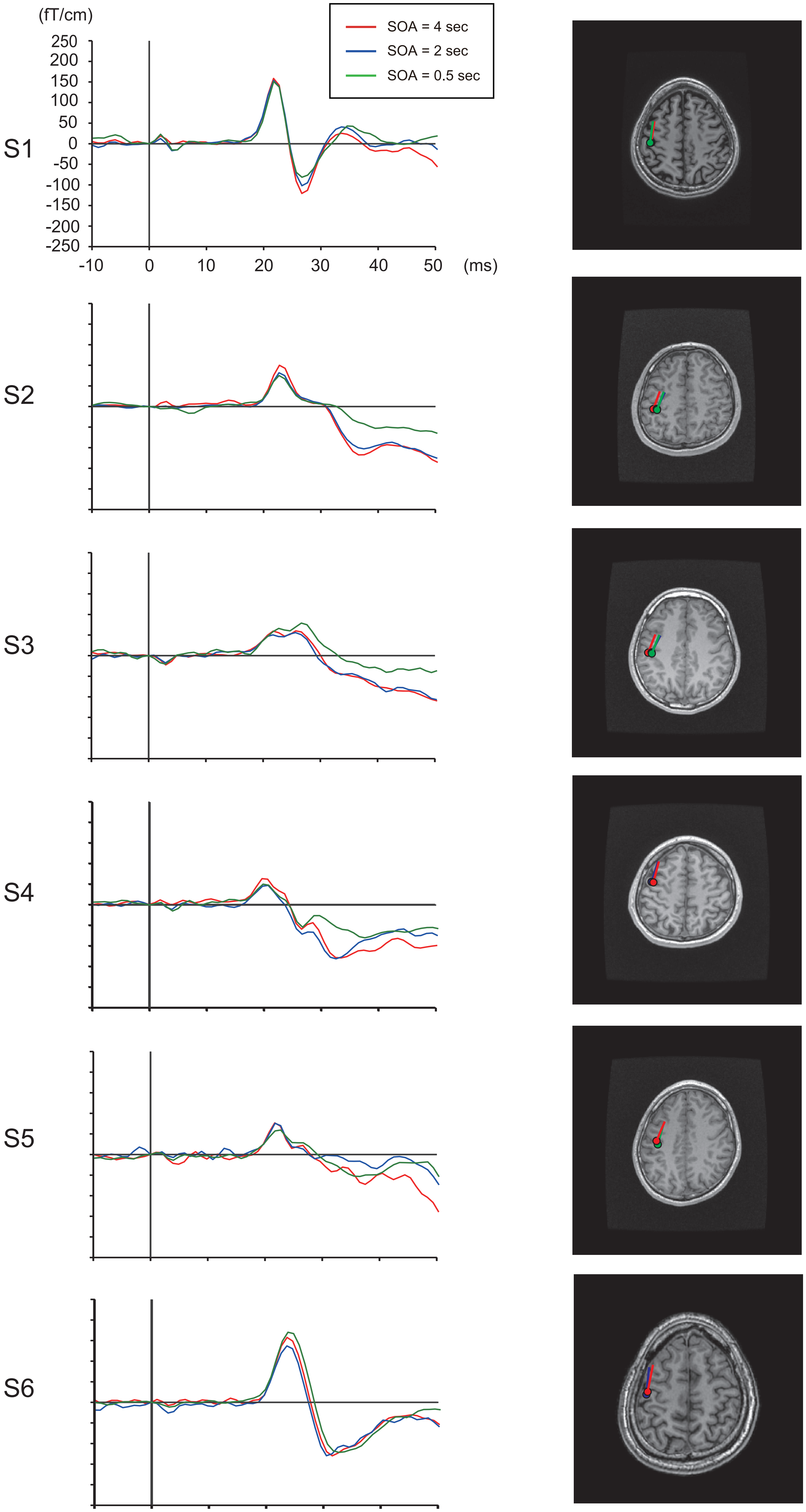
A. Single Channel Analysis



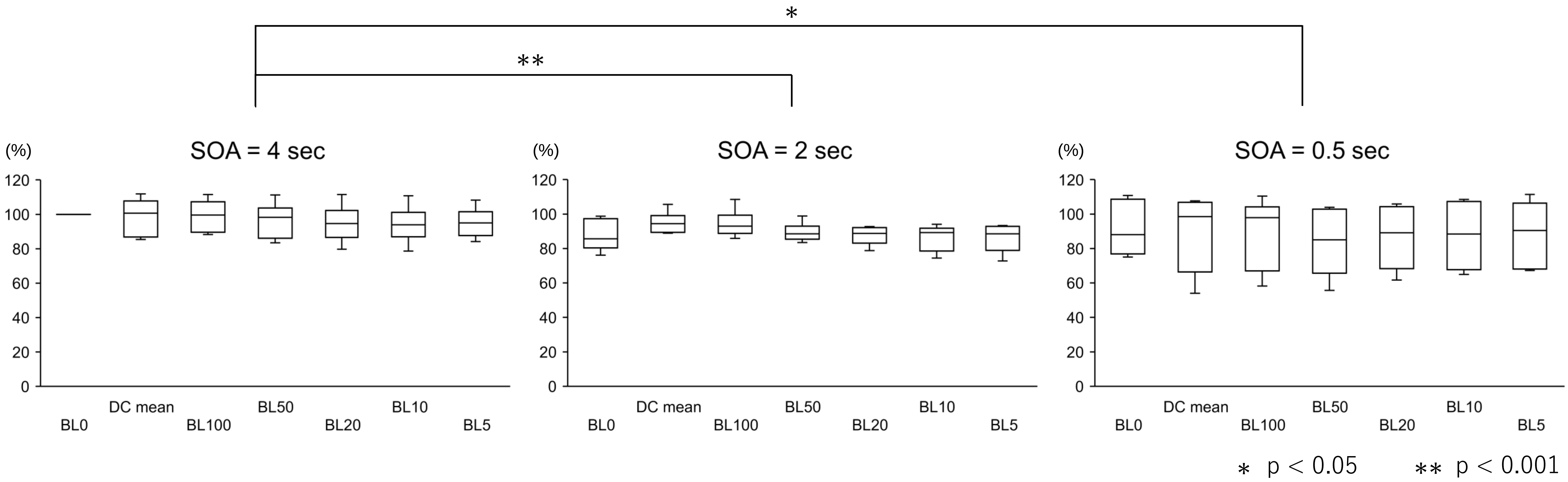
B. Multichannel Analysis

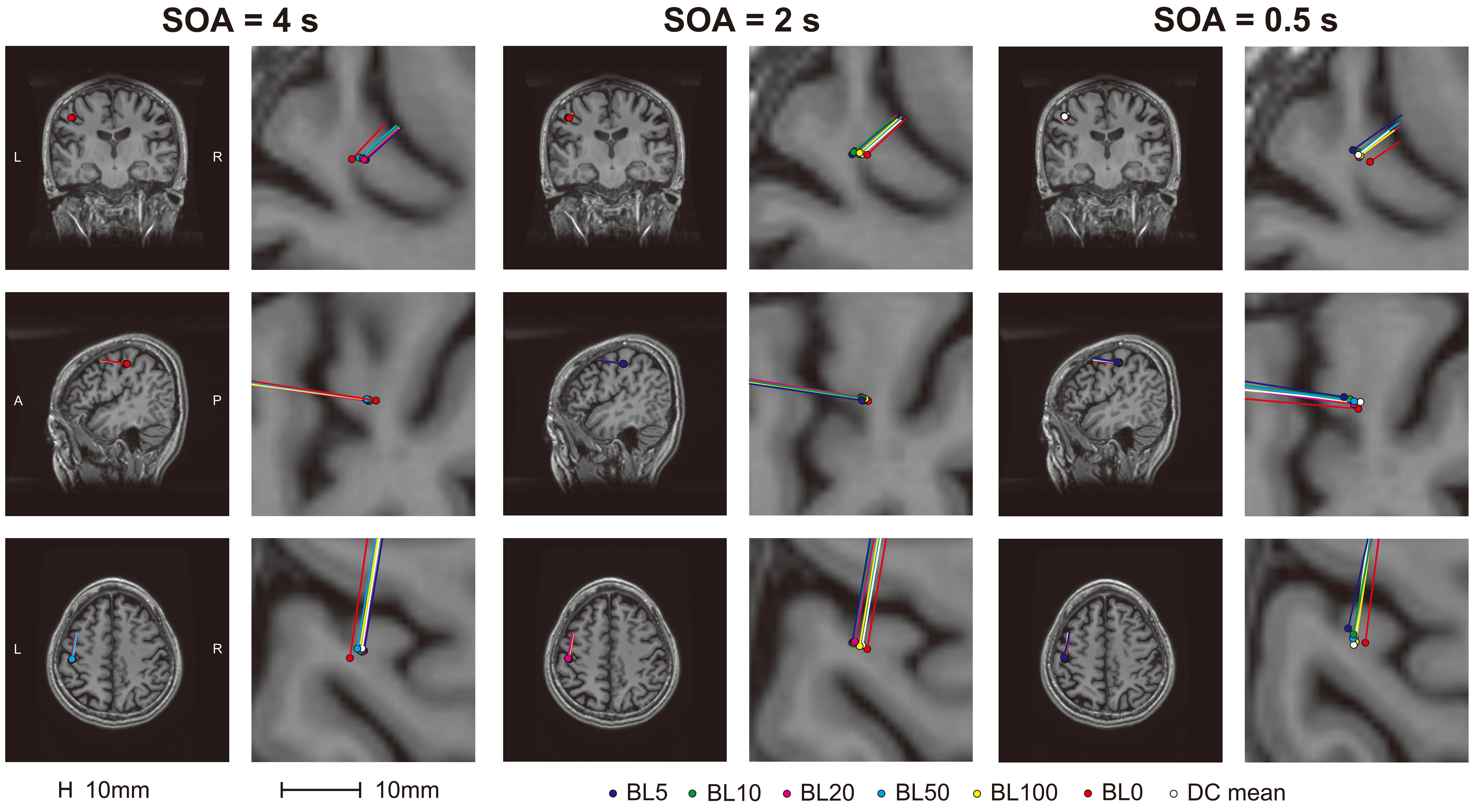



A. within-group reference
SOA = 4 sec
SOA = 2 sec
SOA = 0.5 sec
(mm)
88
85
10.5
7
-46.5
-43
(mm)
5%
10%
20%
50%
100%
DC mean
BL0
ECDm
ECDm
(-45.3, 8.6, 85.7)
ECDm
(-43.9, 8.1, 85.6)
ECDm
(-44.7, 9.2, 87.4)
B. Overall common reference
ECDBL0-4s
ECDBL0-4s
(-45.1, 7.1, 85.6)

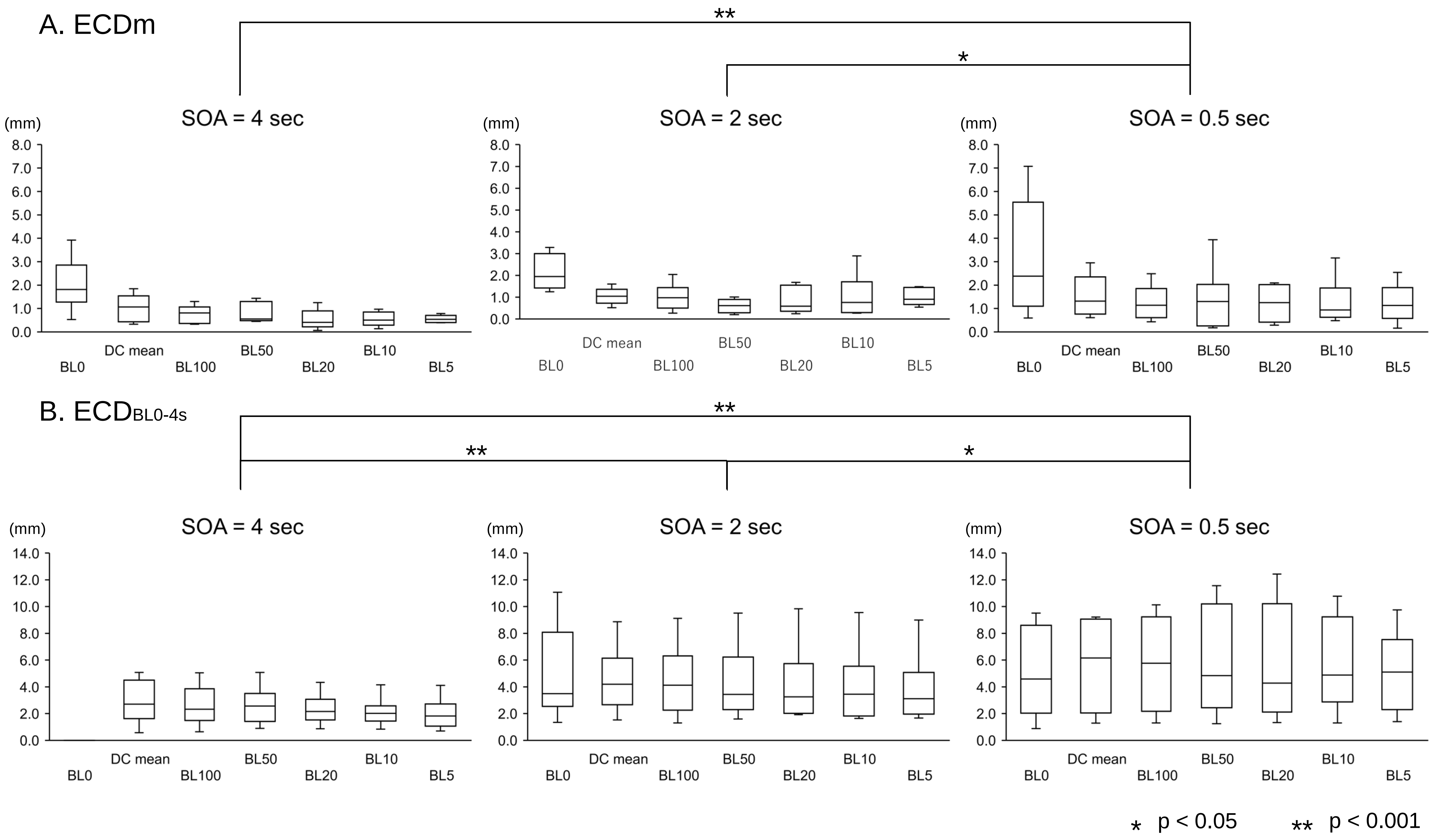


(fT/cm)
SOA = 4 sec
SOA = 2 sec
SOA = 0.5 sec
250
200
150
100
50
0
-50
-100
-150
-200
-250
-10
0
10
20
30
40
50
(ms)
S1
S2
S3
S4
S5
S6


*
**
SOA = 4 sec
SOA = 2 sec
SOA = 0.5 sec
(%)
120
100
80
60
40
20
0
BL0
DC mean
BL100
BL50
BL20
BL10
BL5
* p < 0.05
** p < 0.001



SOA = 4 s
SOA = 2 s
SOA = 0.5 s
L
R
A
P
L
R
H 10mm
10mm
BL5
BL10
BL20
BL50
BL100
BL0
DC mean


A. ECDm
**
*
SOA = 4 sec
SOA = 2 sec
SOA = 0.5 sec
(mm)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
BL0
DC mean
BL100
BL50
BL20
BL10
BL5
B. ECDBL0-4s
**
**
*
(mm)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
* p < 0.05
** p < 0.001

CRediT authorship contribution statement

Hidekazu Saito: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing -review & editing. **Shogo Yazawa:** Conceptualization, Data curation, Investigation, Visualization, Writing - original draft, Writing -review & editing. **Jun Shinozaki:** Conceptualization, Writing -review & editing. **Takashi Murahara:** Conceptualization, Investigation, Writing -review & editing. **Hideaki Shiraishi:** Resources, Writing -review & editing. **Masao Matsuhashi:** Formal analysis, Funding acquisition, Resources, Writing -review & editing. **Takashi Nagamine:** Conceptualization, Funding acquisition, Project administration, Visualization, Writing - original draft, Writing -review & editing.

Declaration of Competing Interest

M.M. belongs to Department of Epilepsy, Movement Disorders and Physiology, Kyoto University which is the Industry-Academia Collaboration Courses, supported by Eisai Co., Ltd., Nihon Kohden Corporation, Otsuka Pharmaceutical Co., Ltd. and UCB Japan Co. Ltd. Other co-authors have no competing interests to declare.