1. Introduction

Intensity of neuromagnetic signals ranges from $10^{-14}$ tesla (T) to $10^{-12}$ T, which is approximately billionth part of earth’s magnetism and millionth part of that of magnetic noises in cities. Magnetoencephalography (MEG) measures such very weak neuromagnetic signals directly related to intracellular electrical currents caused by neuronal activities, so that MEG enables us to detect neural activities with temporal resolution as high as millisecond order [1]. SQUID sensors are used as neuromagnetic sensors, which have sufficient sensitivity as high as approximately $10^{-12}$ T/√Hz (white noise). MEG estimates neural current generators more precisely than electroencephalography (EEG). Because magnetic reluctance of the body tissues is uniform, neuromagnetic signals fit better with simple conductance models of the skull for analyses, whereas electric conductance of the body tissues is not uniform. Utilizing the precision, MEG is used for neuroscientific researches and neurological evaluations such as functional neuroimaging and evaluation of epileptic foci [2]. Most recently, neural decoding techniques have been introduced in the field of MEG to facilitate the effectiveness of neurorehabilitation [3].

In this paper, we describe the recent progress in our MEG research on clinical application regarding functional neuroimaging and neural decoding based on neuromagnetic recordings.

2. Backgrounds

2.1 Cerebral Oscillatory Changes

Synchronous oscillations in specific frequency bands such as alpha waves are well known as basic brain rhythms. These basic rhythms change signal power due to brain activation. Event-related desynchronization (ERD) is an attenuation of the oscillation amplitude of a specific frequency band that occurs in relation to specific neural activities [4]. The opposite phenomenon, event-related synchronization (ERS), is an increase in that amplitude [5].

Synchronous oscillations can be measured using EEG, MEG and electrocorticography (ECoG) which is neural activities recorded from electrodes directly placed on the brain surface. Figure 1 shows the time-frequency spectrograms of ECoGs during right hand grasping. The ECoGs are recorded from grid electrodes placed over the left sensorimotor areas of the human brain. ERDs are observed in the 8–25 Hz (α and β bands) over the sensorimotor areas broadly, whereas ERSs are observed in the 50–200 Hz (high γ band) in the sensorimotor areas more focally. Regarding time domain also, ERDs occur 500–1000 ms prior to muscle contraction and sustained even after the end of muscle contraction, whereas ERSs occurs more strictly during muscle contraction. ERS in the high γ band is known to reflect functional localization of the brain better than ERD in the α and β bands. These oscillatory changes during movements are called as movement-related cerebral oscillatory changes. Cerebral oscillatory changes are observed not only during movements, but also during language activities, sensory processing and mental concentration. ECoG provides us with precise neural activities directly from brain surface electrodes, but needs brain surgery. MEG is noninvasive as well as precise in functional localization.

2.2 Conventional Methods for MEG Analyses

Averaged waveforms, isomagnetic fields, and equivalent current dipoles (ECDs) are conventional methods for MEG analyses. Averaged waveforms are used to detect weak neuromagnetic activities by improving signal-to-noise ratio by averaging time-locked signals. They are appropriate for detecting relatively short latency activities less than several hundred milliseconds. Isomagnetic fields estimate rough
localization of an electric current generator from the distribution of inflow and outflow magnetic fields. An ECD estimates the localization, magnitude and direction of an electric current generator quantitatively as an electric dipole equivalent to the distribution of inflow and outflow magnetic fields based on the Biot-Savart law. These methods enable us to grasp neural activities based on relatively simple principles, while they have several disadvantages. First, for example, when we detect evoked responses to specific stimuli using averaged waveforms, averaging process improves signal-to-noise ratio of the short latency responses. In contrast, high frequency components tend to be lost in the late latency, because the phases of neural responses in the latency might vary from a stimulus to a stimulus, which is a typical characteristic of biological responses. Second, an ECD estimates an electric current generator as a point. However, higher brain functions such as language and cognitive functions activate multiple brain areas simultaneously. ECD has some difficulty in estimating such complex spatial distribution.

2.3 Adaptive Beamformer

To overcome these issues, various methods to estimate complex spatial distribution of neural activities have been introduced. Adaptive beamformer is a spatial noise filtering method and it is used to estimate complex spatial distribution of neural activities from unaveraged MEG signals [6]. Compared with conventional methods, adaptive beamformer takes advantages as follows: 1) high spatial resolution by statistical spatial filtering, 2) ability to elucidate the activities in the high frequency bands and in the late latency without averaging.

Adaptive beamformer assumes the matrix of each voxel within region of interest (ROI) as a virtual sensor array, and estimates source power for each voxel by minimizing signal power due to all other sources. The spatiotemporal MEG signal \( \mathbf{M} \) can be written in matrix form:

\[
\mathbf{M} = [m_{ik}] \\
i = 1 \sim M, \quad k = 1 \sim K
\]

\( M \): number of sensors

\( K \): number of time samples

\( m_{ik} \) is a function of the current \( \mathbf{J} \) throughout the head volume \( \Omega \):

\[
m_{ik} = \int_{\Omega} \mathbf{J}(\mathbf{r}) \cdot \mathbf{G}_i(\mathbf{r}) d\mathbf{r} + n_{ik}
\]

where Green’s functions \( \mathbf{G} \) are used to represent the sensitivity of each sensor to current flow, and \( n \) is the instantaneous noise at sensor \( i \). The sensor variance is represented by diagonal matrix \( \Sigma \):

\[
\Sigma = \begin{bmatrix}
\sigma_1^2 & 0 & \cdots & 0 \\
0 & \sigma_2^2 & \cdots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & \sigma_M^2
\end{bmatrix}
\]

The source power estimate \( S_\theta \) is:

\[
S_\theta^2 = [\mathbf{H}_\theta^T \mathbf{M}]^2
\]

\( \mathbf{H} \): a vector of \( M \) beamforming coefficients

\( \mathbf{M} \): the signal space vector

\( \theta \): the target within brain.

The source noise variance is estimated:

\[
\sigma_\theta^2 = \mathbf{H}_\theta^T \Sigma \mathbf{H}_\theta
\]

Two additional constraints are required for solution of the beamforming coefficients. First, power \( S \) must be a measure of source and not signal:

\[
\mathbf{H}_\theta^T \mathbf{G}_\alpha \equiv 1
\]

Second, uncorrelated noise will appear in the source power
estimate of Eq. (5). This constraint sets an upper limit on the noise:

$$\sigma_\theta \leq \xi_\theta$$  \hspace{1cm} (7)

The beamformer coefficients are computed by minimizing source power (Eq. (4)):

$$S_\theta^2 = H^T_\theta C H_\theta$$  \hspace{1cm} (8)

$$\min H$$

$C$: the covariance matrix.

Thus, the source power estimate solution becomes:

$$S_\theta^2 = [G_\theta^T [C + \mu \sum G_\theta]^{-1} G_\theta]^{-1}$$  \hspace{1cm} (9)

$\mu$: a Backus-Gilbert regularization parameter.

2.4 Group Analyses

We introduced group analyses to obtain common brain activities among subjects eliminating inter-individual differences (Fig. 2) [7].

Group statistical maps are generated by normalizing the individual results to standard space and then combining these results across subjects for each frequency band. First, each individual’s anatomical MRI is resliced to the same orientation and position as the beamforming MEG results and statistical parametric mapping is used to find the transformation matrix from this functional space into the Montreal Neurological Institute (MNI) template. The transformation matrix is then applied to each of the beamforming MEG results in each frequency band, and for each subject. A permutation test is used to generate group statistical maps over each voxel in the standard brain using statistical non-parametric mapping (SnPM; Wellcome Department of Imaging Neuroscience, London, UK). Analysis at the voxel level was performed using a pseudo-T-statistic incorporating variance smoothing with a Gaussian kernel of width 8 mm. These group statistical maps were then thresholded at $p < 0.001$ (corrected), and superimposed on the MNI template brain using mri3dX (CUBRIC, Cardiff, UK).

2.5 Neural Decoding

Neural decoding is a method to infer the content of behavior or cognition from brain signals alone. Progress of functional brain researches has enabled us to neural decoding. Various methods are used for neural decoding. Here, we show a support vector machine (SVM) [8], which we use to decode neuromagnetic signals during upper hand and arm movements in our study [9].

An SVM is a learning machine which is often used for pattern recognition. It constructs a hyperplane or set of hyperplanes in a high- or infinite-dimensional space, which can be used for classification, regression, or other tasks. Intuitively, a good separation is achieved by the hyperplane that has the largest distance to the nearest training data point of any class, so-called functional margin, since in general the larger the margin the lower the generalization error of the classifier (Fig. 3). An SVM takes a set of input data and predicts, for each given input, which of multiple possible classes forms the input, making it a non-probabilistic classifier. Given a set of training examples, each marked as belonging to one of multiple categories, an SVM training algorithm builds a model that assigns new examples into one category. An SVM model is a representation of the examples as points in space, mapped so that the examples of the separate categories are divided by a clear gap that is as wide as possible. New examples are then mapped into that same space and predicted to belong to a category based on which side of the gap they fall on.
3. Neuromagnetic Imaging of Cerebral Oscillatory Changes

3.1 Somatosensory Processing

Typical neuromagnetic somatosensory responses are observed when we stimulate major peripheral nerves of the body. We measured neuromagnetic responses using a whole head type axial gradiometer equipped with 64 SQUID sensors. Figure 4 shows the averaged waveforms of the somatosensory responses of all 64 SQUID sensors for 100 electrical stimuli to the right median nerve at the wrist in a healthy subject. Clear responses are observed in 20 ms, 26 ms, 39 ms and 51 ms after the stimuli. Isomagnetic field maps show clear inflow and outflow of neuromagnetic fields. A current dipole equivalent to the magnetic field at 20 ms after the stimuli is localized just in the contralateral post-central gyrus. The postcentral gyrus is well known as the primary somatosensory area, where somatosensory processing such as touch and vibration sensation of the body.

Beamformer analyses provide us with additional information about spatiotemporal distribution of neural processing. Beamformer analyses show the distributed ERS in the contralateral somatosensory area in the high \( \gamma \) band (50–200 Hz) as well as the ERDs in the bilateral somatosensory areas in the \( \alpha \) (8–13 Hz) and \( \beta \) (13–25 Hz) bands (Fig. 5) [10]. These ERDs and ERS are suggested to reflect inhibitory and excitatory neural activities related to somatosensory processing.

3.2 Language Processing

Compared to somatosensory processing, neuromagnetic responses to linguistic stimuli are more complex. We use a silent reading task to avoid the noise contamination due to muscle contraction during phonation. A 3-character hiragana word was presented on a display for 3 seconds. Subjects are instructed to silently read the words once as soon as the words were presented. A total of 100 words were presented serially every 6 seconds. Figure 6A shows the averaged waveforms of neuromagnetic responses of all 64 SQUID sensors for visually-presented hiragana words in a healthy subject. They have later latency components and isofield maps indicate more complex inflow and outflow distribution than those of somatosensory processing (Fig. 6B).

Single ECD analyses managed to localize an ECD until 330 ms, but represented only part of the complex neuromagnetic fields. Multiple ECD analyses failed to localize stable ECDs with sufficient goodness of fit.

Beamformer analyses provide us with complex spatial distribution of cerebral oscillatory changes during silent reading. Figure 7 shows the result of group analysis for 14 healthy right-handed subjects. It is noteworthy that the spatiotemporal distribution of cerebral oscillatory changes during silent reading.
tial distribution is dependent on the frequency bands of the oscillatory changes. ERDs in the $\alpha$ band distributed in the posterior (receptive) language area, whereas ERDs in the low $\gamma$ band distributed in the frontal (expressive) language area [7]. In addition, we found that the left and right lateralization of ERD in the frontal area in the low $\gamma$ band well corresponds to language dominance [11]. Using this property, we established the method to evaluate language dominance noninvasively with beamforming MEG analyses. Compared to the standard but invasive method for language dominance (the Wada test) which requires the injection of anesthetic agents intra-arterially at the carotid artery, the consistency is approximately 85% [7]. Beamforming MEG analysis is considered to be an alternative to the Wada test in selected cases. Figure 9 shows an example of language dominance evaluated by this method.

Sliding time window analyses of beamforming MEG revealed the temporal profiles of cerebral oscillatory changes during silent reading (Fig. 8) [12]. We found that the transient ERS first occurred in the occipital visual area, then in the temporo-occipital language areas, and finally propagated to the frontal language areas. This transient $\theta$ (8–13 Hz) ERS was followed by $\alpha$ ERDs in the temporo-occipital language areas and low $\gamma$ ERDs in the frontal language areas. High $\gamma$ ERS was found in the occipital lobe, which reflects visual processing. It seems that transient $\theta$ ERS reflects serial processing while $\alpha$ and low $\gamma$ ERDs reflect parallel neural processing.

Beamforming MEG group analyses well represent frequency-dependent complex spatial distribution of cerebral oscillatory changes during silent reading. ERDs in the $\alpha$ band distributed in the receptive language area, whereas ERDs in the low $\gamma$ band distributed in the expressive language area.

Fig. 6 Neuromagnetic responses during silent reading.

Fig. 7 Spatial distribution of cerebral oscillatory changes during silent reading revealed by beamforming MEG group analyses for 14 healthy right-handed subjects.

A. Averaged waveforms
B. Isofield maps
C. Equivalent current dipoles (ECDs)

Compared to somatosensory responses, averaged waveforms have late latency components and isofield maps indicate complex inflow and outflow distribution. Single ECD represents only part of the complex neuromagnetic fields. However, multiple ECD analyses failed to localize stable ECDs with sufficient goodness of fit.
4. Neural Decoding of Upper Limb Movements Using Single Trial Neuromagnetic Signals

We investigated neural decoding of upper limb movements using single trial neuromagnetic signals. Neuromagnetic activities were recorded in 9 healthy subjects during 3 types of unilateral upper limb movements. The movement types were inferred by a SVM. A one-way analysis of variance (ANOVA) was performed to reveal the spatiotemporal differences in the magnetic fields among the three movements. Significant F values in all MEG channels were calculated using the same parameters used for calculating the time course of the decoding accuracy. The topographies of the F values were delineated on a map of MEG sensors to determine which channels exhibited significant differences in neuromagnetic activities among movements.

The movement types were successfully predicted with an average accuracy of 66 ± 10% (chance level: 33.3%) using neuromagnetic activity during a 400-ms interval (−200 ms to 200 ms from movement onsets) [13]. Figure 10A shows the temporal profiles of averaged waveforms of normalized magnetic fields and decoding accuracy in a representative subject. Three peaks of decoding accuracy were found corresponding to the peaks of averaged waveforms of neuromagnetic fields. Topography of F values showed that high F values distributed over the parietal and sensorimotor areas (Fig. 10B). The decoding accuracy was significantly correlated with amplitude of normalized neuromagnetic fields [9].

Our results indicate that the three types of unilateral upper limb movement can be inferred with high accuracy by detecting differences in movement-related brain activity in the parietal and sensorimotor areas.

5. Conclusion

We reviewed the recent progress in our MEG research on clinical application regarding functional neuroimaging and neural decoding using neuromagnetic recordings. Beamforming MEG analyses provide us with frequency-dependent spatiotemporal information about the cerebral oscillatory changes related to not only somatosensory processing but also language processing. Language dominance is able to be evaluated using laterality of the low γ ERD in the frontal area. Neuromagnetic signals of the unilateral upper movements are able to be decoded using a SVM.

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Fig. 10  Neural decoding of upper limb movements using single trial neuromagnetic signals.

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