35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Non-parametric permutation thresholding for adaptive nonlinear beamformer analysis on MEG revealed oscillatory neuronal dynamics in human brain

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Abstract— **Adaptive nonlinear beamformer technique for analyzing magnetoencephalography (MEG) data has been proved to be powerful tool for both brain research and clinical applications. A general method of analyzing multiple subject data with a formal statistical treatment for the group data has been developed and applied for various types of MEG data. Our latest application of this method was frontal midline theta rhythm (Fmθ), which indicates focused attention and appears widely distributed over medial prefrontal areas in EEG recordings. To localize cortical generators of the magnetic counterpart of Fmθ precisely and identify cortical sources and underlying neural activity associated with mental calculation processing (i.e., arithmetic subtraction), we applied adaptive nonlinear beamformer and permutation analysis on MEG data. As a result, it was indicated that Fmθ is generated in the dorsal anterior cingulate and adjacent medial prefrontal cortex. Gamma event-related synchronization is as an index of activation in right parietal regions subserving mental subtraction associated with basic numerical processing and number-based spatial attention. Gamma desynchronization appeared in the right lateral prefrontal cortex, likely representing a mechanism to interrupt neural activity that can interfere with the ongoing cognitive task. We suggest that the combination of adaptive nonlinear beamformer and permutation analysis on MEG data is quite powerful tool to reveal the oscillatory neuronal dynamics in human brain.**

I. Introduction

The magnetic field generated in the brain is quite less influenced by anatomical structures such as skin, skull, dura matter and the cerebrospinal fluid, so magnetoencephalography (MEG) can identify neural sources accurately and non-invasively. Because of the detector positioning of MEG system and anatomical differences between subjects, the MEG data cannot be combined easily among different subjects.

The beamformer method has been originally developed for signal detection in the radar applications [1], and recently being adapted for source estimations in MEG. Adaptive nonlinear beamformer can act as a spatially selective filter to MEG signals to bring us the considerable insight into the dynamics of oscillatory activity across the cortex. By using this method, we can estimate the oscillatory activity coming from a given location in the brain [2]. The accuracy of this map relies on the correctness of the beamformer assumptions for the given data set [2-5].

The permutation test has been commonly applied to wide range of data analysis. As a non-parametric test, permutation test does not rely on any assumption about the data distribution. It is robust tool to determine the statistical significance of the data with the absence of a reliable parametric alternative [6]. Without any knowledge about how the estimated sources distribute in the brainacross subjects, it becomes natural to use a non-parametric test, like permutation test, to determine the significance of the detected sources for group analysis. The concept of permutation test is based on the fact that if the effects of two or more conditions in an experiment are not different, then the test results would remain the same even the condition labels have been changed randomly. Since we performed permutation tests on neuroimaging data, an empirical null distribution, which was free from any activated voxels, was necessary. We used a "step-down" procedure to determine the distribution by iteratively recomputing it when a possible activated voxel was found with the current distribution. The distribution has to be recomputed for each one of the activated voxels.

By applying this method combined with non-parametric permutation tests for statistical group analysis of MEG data, we could accurately identify neural sources functionally engaged in perceptual information processing [7], the preparation and the act of swallowing [8], the generator of sleep spindle [9], cortical organization of sensorimotor areas [10], activation in the primary somatosensory cortex [11], neural correlate related to theory of mind [12], the executive function of bilingual subjects [13], singing and vocalization [14] and the magnetic counter part of P300 component related to auditory attention and memory updating process [3].

Frontal midline theta rhythm (Fmθ) was firstly reported as an EEG phenomenon related to focused attentional processing by Ishihara and Yoshii in 1972 from Osaka University [15]. This activity is a distinct train of focal 5-7 Hz theta waves which appears over medial frontal areas in the EEG of normal subjects when performing a broad range of cognitive tasks demanding mental concentration [15]. Although previous studies of Fmθ using EEG reported widespread distribution of this activity in middle frontal area, it was still lacking that no EEG study identified its cortical generators within the medial frontal cortex accurately [16-18] because of its low spatial resolution. By using MEG to visualize its cortical sources of the magnetic counterpart, we previously reported that MEG depicted a large area over the bilateral medial prefrontal cortex

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978-1-4577-0216-7/13/$26.00 ©2013 IEEE

generated Fmθ during continuous mental calculation in four normal subjects [2]. Thus, our findings provided further support for a specific role of the prefrontal cortex in focused attentional processing.

In this study, we aimed to utilize adaptive nonlinear beamformer analysis, SAM (synthetic aperture Magnetometry), and non-parametric permutation analysis to depict the cortical generators of the magnetic counterpart of Fmθ during focused attention and to identify cortical sources and underlying neural activity associated with mental calculation, particularly with arithmetic subtraction.

II. METHODS

A. MEG measurement

We enrolled eleven healthy volunteers (six males, aged 27-36 years, mean age 32 years, all right-handed) in this study. We obtained informed consent from all subjects prior to the experiments. The study was performed in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Osaka University Hospital. The experiment consisted of two conditions: 1) mental calculation or arithmetic state (active interval) and 2) eye-closed resting state (control interval). When we identified rhythmic theta oscillations lasting for at least 10 sec visually in the MEG recordings, a beeping sound was given to indicate the end of the arithmetic state and the beginning of the resting state for 10 sec. Thus, resting and mental calculation states were alternately recorded on each subject for a total of 8 trials, each one of 20-sec duration. We performed MEG recordings on all subjects in a magnetically shielded room using a helmet-shaped 64-channel SQUID sensor array (NeuroSQUID Model 100, CTF Systems Inc.). MEG signals were digitized at a sample rate of 250 Hz, and filtered using a 60 Hz notch filter and 100 Hz low pass filter. The resulting data were recorded on disk and analyzed offline. We obtained magnetic resonance imaging (MRI) scans were for all subjects using a 1.0-T MRI system (Magneton Impact, SIEMENS Inc., Germany) or a 1.5-T Siemens Magnetom Vision plus system (Siemens, Erlangen, Germany) to convert the sources of MEG oscillatory activities into subjects' brain images.

B. Adaptive nonlinear beamformer analysis

Basic concept of SAM is the beamforming technique which is commonly used in sonar and radar for signal detection. To suppress the interference of the unwanted signals, SAM applies a spatial filter, specific for each location in the head, as an adaptive nonlinear beamformer. Although the details of SAM algorithms were already introduced in our previous publications [4, 19], we summarize this here briefly.

Three-dimensional volume of the distribution of source powers is obtained by applying the following procedure at each location inside the head. The spatial filter at location θ is a linear projection operator defined by a set of coefficients (W_θ):

$$W_\theta = \frac{[C + \mu\Sigma]^{-1} B_\theta}{B_\theta^T [C + \mu\Sigma]^{-1} B_\theta} \quad (1)$$

where Σ is a diagonal matrix representing the estimated sensor noise power, C is the covariance matrix between the sensor signals, and B_θ is the forward solution due to a dipole located at θ, and μ is the Backus-Gilbert regularization parameter adjusting the tradeoff between the filter's spatial resolution and sensitivity to the uncorrelated noise. With μ=0, the obtained coefficients are the minimum-variance solution which has maximum spatial selectivity; whereas, minimum-norm solution is obtained when μ is very large. After the coefficients have been determined, the power of the filtered signal is then computed using equation:

$$S_\theta^2 = [W_\theta^T M]^2 = W_\theta^T C W_\theta \quad (2)$$

With one coefficient for each sensor, which is determined by minimizing the source power, subject to the constraint of $W_\theta^T B_\theta = 1$, where M is the measurements. Due to the constraint of $W_\theta^T B_\theta = 1$, which has the effect of normalizing the filtered signal to units of source strength, and lower the signal-to-noise ratio with depth, the estimated source power is increased with depth. To better determine the source distribution, the relative strength of the source power and noise is used to generate the brain volume. With a single active task, the ratio of source power to noise can be used; whereas with active and control tasks, the ratio of the power differences between the active and control tasks to the sum of the powers of noise [8] can be used:

$$T_\theta = \frac{S_\theta^A - S_\theta^C}{N_\theta^A - N_\theta^C} \quad (3)$$

where S_θ^A and S_θ^C is the estimated power of the source for the active and control task, respectively, N_θ^A and N_θ^C are the estimated powers of the noise.

C. Spatial Normalization

To convert subject data to a common anatomical space, we utilized SPM99. First of all, we converted subject's SAM volume and the MR image to the ANALYZE image format, which is the native image format for SPM99. Second, the SAM volume is coregistered to the MR image based on the position of the fiduciary markers. Third, the spatial normalization parameters are determined by transforming the subject's MR image to a common anatomical space using SPM99. Fourth, the spatial normalized subject data are subsequently obtained by applying the above transformation to the SAM volume.

D. Permutation Test for Group Analysis

The procedure for the permutation test includes following steps. First, we selected a test statistic which measures the differences between conditions. Second, we computed the test statistic for the original condition labeling. Third, we randomly rearranged the condition labels and compute the test statistic for the permuted data. Fourth, we repeated step 3

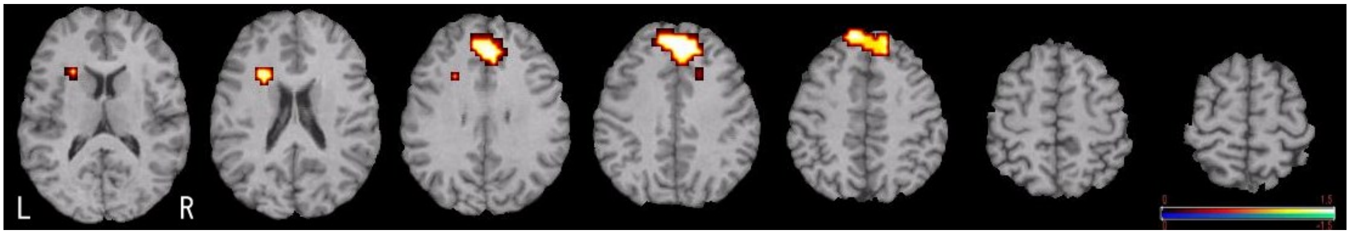

Fig 1. SAM-permutation images of source power changes (event-related synchronization) in the theta (4–8 Hz) band. Responses were calculated for the mental calculation (active state) versus non-arithmetic condition (control state). The color bar represents pseudo-t values. L, left; R, right.

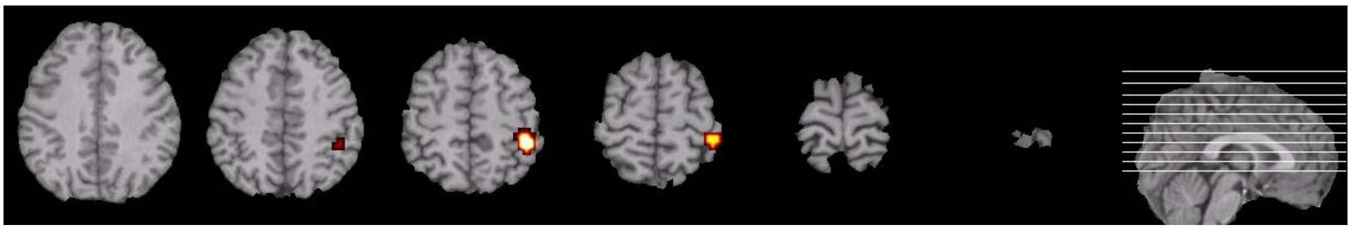

Fig 2. SAM-permutation images of source power changes (event-related synchronization) in the gamma (30-60 Hz) band. Responses were calculated for the mental calculation (active state) versus non-arithmetic condition (control state).

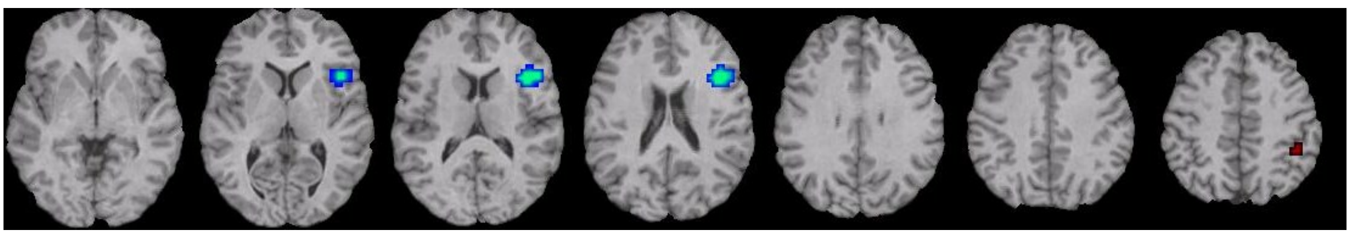

Fig 3. SAM-permutation images of source power changes (event-related desynchronization) in the gamma (30-60 Hz) band. Responses were calculated for the mental calculation (active state) versus non-arithmetic condition (control state).

until a predefined number of permutations has been performed. Fifth, we compared test statistic from permuted data to the original data. Sixth, we accepted or rejected the hypothesis based on the proportion of permuted test statistics equal to or greater than the original. MEG measurements were performed during the active condition under which the stimulus is presented to the subject and control condition at the resting state. With only two conditions for each subject measurement, the total number of possible rearrangement of the conditions would be 2^N for N subjects. For example with 10 subjects, maximum of 1024 permutations can be performed, which is sufficient to obtain a reliable result [5].

Since the estimated source strength might be different between subjects, not all subjects contribute equally to the test statistic if the simple summation of T_θ defined in Eq. (3) was used. We avoided this problem by standardizing T_θ by the standard deviation of T_θ within each subject volume. We used the sum of these standardize T_θ values for test statistic. First we computed the statistics for all permutations, and then the original standardized T_θ value for each location was compared against the permutation results.

We avoided the activated voxels spoiling the null distribution by performing an iteration procedure. First, a null distribution was build by using the maximum absolute values of the resampling mean pseudo-t SAM volumes. Second, for a given p value, the value of each voxeT in the original mean SAM volume is compared against with the current null distribution. If there were less than p% of the null distribution had larger pseudo-t value than that of current voxel, the voxel was considered to be active and will be excluded for using to construct the distribution. The updated null distribution was constructed without any previously identified active voxels. By repeating the process of identifying the activated voxels and reconstructing the null distribution, the final null distribution was found when there were no more active voxel being detected.

III. RESULTS

Only in theta and gamma frequency bands over different cortical regions showed significant source-power changes during focusing attention on mental calculation. The visual inspection of the MEG recordings revealed increased rhythmic theta activity at around 5-7Hz when the subjects were engaged in mental calculation compared to the resting condition. The permutation test results indicated a significant increase in theta activity in the medial prefrontal cortex (BAs 8 and 9) and the adjacent dorsal part of the ACC (BA 32) during periods of focused attention on mental calculation (Fig 1). It was also revealed that gamma activity (30-60Hz) exhibited both significant ERS and ERD during the mental calculation periods. Gamma ERS was observed in the right intraparietal sulcus (IPS) and the adjacent posterosuperior and inferior parietal lobules, whereas the ERD was observed over the inferior frontal gyrus (BA 44) in the same hemisphere (Fig. 2, 3).

IV. DISCUSSION

To detect multiple source generators from the MEG data, adaptive nonlinear beamformer is one of the better solutions to the dipole analysis. We showed the procedure of combining the multi-subject MEG beamformer images and investigated the performance of non-parametric permutation tests for group analysis. Through analyzing data of focused attentional experiment, we demonstrated that this combination seems to be quite useful tool to perform group analysis on the MEG data.

Using MEG and SAM-permutation analysis during continuous mental calculation, we clearly identified pronounced theta ERS, representing Fmθ, distributed over bilateral medial prefrontal regions and the dorsal area of the ACC (Fig 1). Most prominent results were the identification of significant gamma power changes, in particular gamma ERS in the right IPS and adjacent cortex, and gamma ERD in the inferior frontal cortex (Fig 2, 3). This suggests that focusing attention on mental calculation results in Fmθ generation and the arithmetic processing of the task also showed the activation of neural networks involving the parietal and lateral prefrontal cortex with power changes in the gamma band.

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