

3-6 Neural Activation Related To Language Processes and An Analysis Method

FUJIMAKI Norio and HAYAKAWA Tomoe

Language has especially been developed in human species, and is indispensable for information and communications technologies. In this review paper, we introduce our researches on measurements of brain functions related to language with functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). We developed a method of analyzing spatial and temporal brain activations with high reliability by using both fMRI data with a fine spatial resolution and MEG data with a fine temporal resolution, and applied it to data of lexical decision, inner speech, and visual search experiments. We measured and separated brain activations for visual-form, phonological, and semantic processes of characters and words. We also measured dependence of brain activations on reading speeds when rapid readers read sentences. Finally we introduce our recent research on semantic and repetition priming experiments and modeling of language brain activations.

Keywords

Language, Neural activation, fMRI, MEG, Inverse problem

1 Introduction

Language is a brain function that has developed uniquely in humans. We use language to perform various types of information processing. A large part of daily thought is performed with language, and a major portion of human culture and civilization owes its existence to language. The brain commands the functions of language, and even with astonishing progress in artificial computing, to date no machine has been designed to match the language processes seen in humans. The mechanism behind this amazing function of the human brain has attracted intense scientific interest, and clarification of this issue will undoubtedly provide important clues in the development of future information-communication technologies.

When characters and words are processed in the brain, lexical processes such as visual-form processes, phonological processes, and

semantic processes are performed. Further, for sentences, in which words are arranged, syntactic processes are also performed. In order to investigate when and where these processes take place, neural activity has been measured using electroencephalography (EEG), positron emission tomography (PET), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and near infrared spectroscopy (NIRS). With these non-invasive methods, neural activity in the brain can be measured from outside of head, enabling a lot of experiments using normal subjects, as opposed to former experimentation limited to animals and patients suffering from brain injuries and diseases. Particularly from the 1990s, with substantial progress in the development of these measurement methods, rapid advances have taken place in brain research, with a number of impressive research results reported to date. Particularly with respect to language functions, which are

difficult to investigate through animal experimentation, non-invasive brain-function measurement is an extremely important investigative tool.

We have been conducting measurement of neural activities relating to reading in Japanese using MEG and fMRI. fMRI offers excellent spatial resolution, while MEG provides precise temporal resolution; each method thus has its merits and drawbacks. We have developed a unique method of combining and analyzing data obtained through these methods, rendering it possible to analyze sources of neural activity with high reliability. This paper summarizes the development of this analysis method and the measurement results of neural activity corresponding to various language processes for simple lines, characters, words, and sentences. We also present an introductory description of our latest priming experiments, and the first steps in future neural modeling.

2 Neural activity during lexical decision

2.1 Experimental task [1]

Language processes consist of multiple processing steps. When characters and words are presented, lexical processes are performed in the brain. Broadly speaking, these processes consist of three types: visual-form processing of characters and orthography, phonological processing (representation of language in sound), and semantic processes at a lexical level. In terms of sentences, the syntactic processes of translating a word arrangement into a semantic concept are additionally required (Fig. 1). It is our belief that in order to clarify the language-processing mechanism in the brain, it will be useful to understand the areas and times of occurrence of the neural activities corresponding to these processes. This chapter describes experiments in which the relation between processing of words and neural activity is investigated.

It would be meaningless if we were to simply present a word visually to a subject

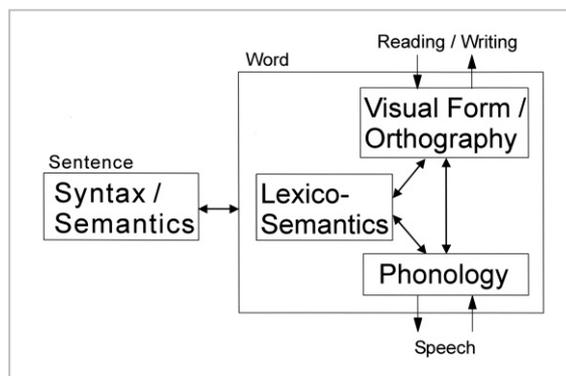


Fig. 1 Language processes in the brain

and ask the subject to execute only one group of processes (visual-form, phonological, or semantic) to measure the neural activity related to the selected group. Because it is known that if the word is recognized, all three groups of processes are performed automatically in the brain. Therefore, we prepared experimental tasks in which processes were included in stages as follows (Fig. 2): judgments as to whether a horizontal line is included in pseudo-characters created by deforming original characters (visual-form processes), judgments as to whether katakana characters include the vowel “a” (visual-form processes + phonological processes), judgments as to whether a character string is a word or is meaningless (visual-form processes + phonological processes + semantic processes). Note that the symbol “ ’ ” to the right of a process in the figure indicates processing of a character string instead of a single character. These tasks are intended to separate neural activity corresponding to an individual group of processes by observing differences in neural activity between these tasks. Detailed research in English-speaking countries has involved experiments using such tasks, but contradictions have been noted among some of the reports. We conducted our experiments using the tasks illustrated in Fig. 2 that make particular use of katakana phonograms (exactly speaking, syllabograms) which are similar to the English alphabet; neural activity was measured using fMRI, with its excellent spatial resolution, and MEG, with its precise temporal resolution (Fig. 3).

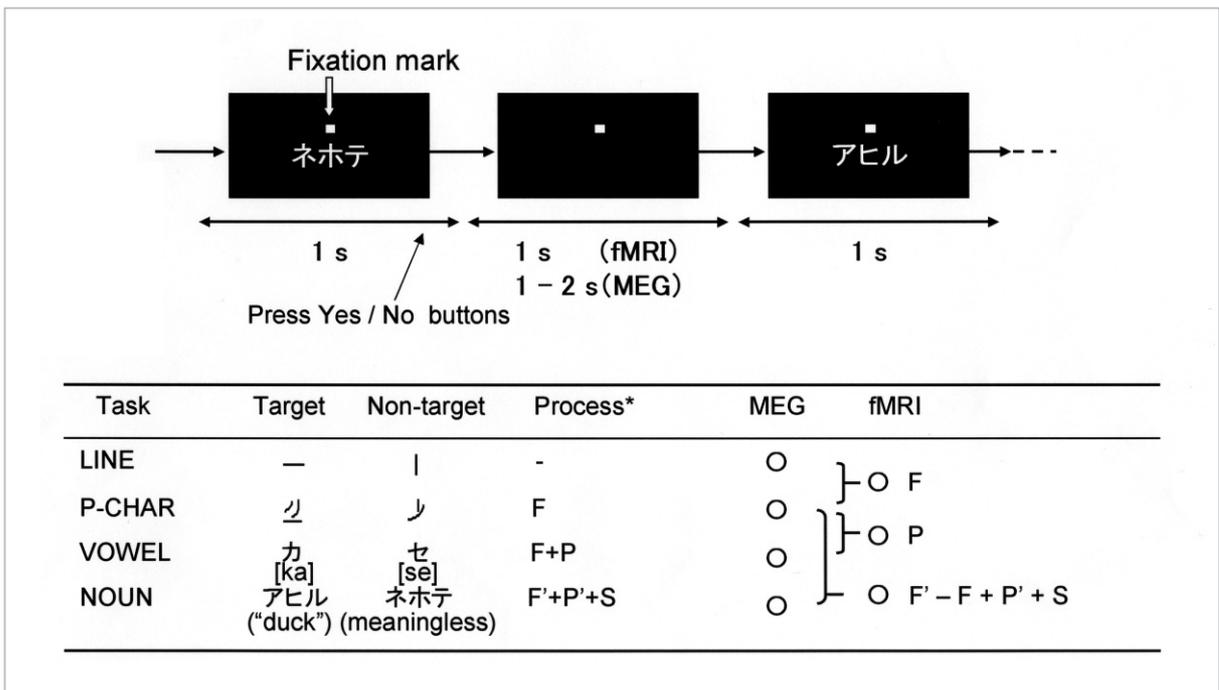


Fig.2 Experimental tasks with characters and words

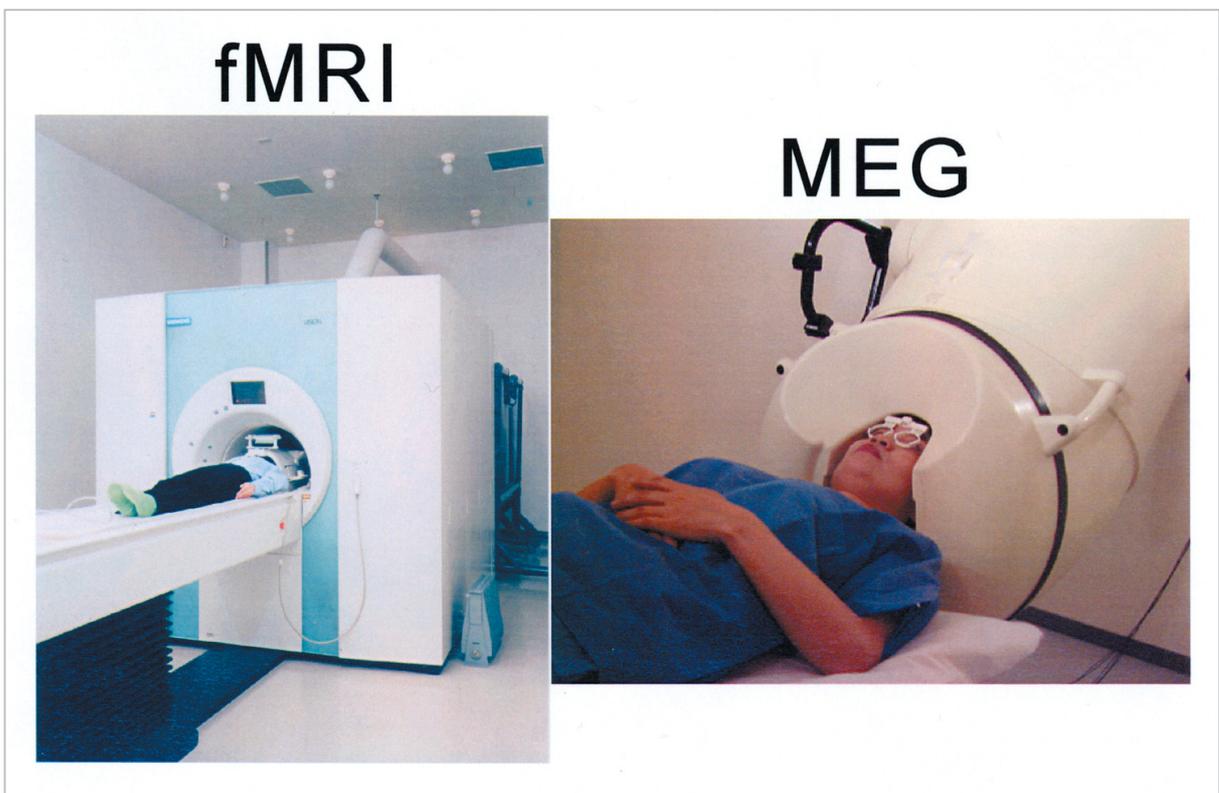


Fig.3 fMRI and MEG system

2.2 fMRI measurement [1]

Our MRI system (Siemens A G, Vision), featuring a magnetic-field strength of 1.5 T, is shown in the left-hand portion of Fig. 3. In

fMRI operation, it records changes in a magnetic resonance signal (Blood Oxygenation Level Dependent, “BOLD”) stemming from changes in blood flow incident to the neural

activity. When the brain is active, the blood flow increases in the active area in order to increase the oxygen supply to this area. Since oxygen is supplied exceeding the amount consumed, the amount of deoxygenated hemoglobin featuring paramagnetic properties (other components and tissues are diamagnetic) will decrease, as will the inhomogeneity of the regional magnetic field. Thus, the apparent transverse relaxation time constant of the magnetic resonance signal will become longer, and the signal will increase by approximately several percent. Normally this hemodynamic mechanism is considered the origin of the magnetic resonance signal changes. It should be noted that the dynamic properties of blood flow are complicated and some objections to this hypothesis have been raised. However, a large number of experiments have been carried out on cerebral functions, and most of the observed results indicating particular areas of activity are consistent with previous brain research. Note that a magnetic field gradient is used in gathering image data, with final images reconstructed through Fourier transform. Using this method, even with multiple sites of neural activity, a spatial distribution (i.e., a functional image) can be obtained with resolution as precise as several millimeters. The MRI system can also provide a structural image by measuring the difference in the relaxation time, which depends on materials. Superimposing these two images enables us to investigate the locations of neural activity in detail. In comparison to PET, in which blood flow changes are also detected, fMRI experiments can be conducted repeatedly on the same subject since no radioactive isotopes are used; fMRI is therefore a less invasive technique than PET.

Since there is a delay of a few seconds or more (hemodynamic delay) before blood flow starts to change after neural activity, fMRI does not feature sufficient time resolution to determine the activity of neural cells. In actual experiments, two or more tasks (featuring different test and control conditions) are assigned alternately for a period sufficiently

longer than the hemodynamic delay for each task (a period lasting, for example, tens of seconds) and the difference in activity between test and control conditions is obtained (this is referred to as “block design”), or a signal waveform responding to the stimulus is measured (event-related fMRI).

This paper describes an experiment based on the block design. Specifically, we performed a cognitive subtraction to determine the location of neural activity corresponding to differences in processes as shown in Fig. 2. Scans were performed every four seconds, with the entire head represented by 16 slices of recorded images. In order to detect small signals despite superimposed noise, 124 scans were taken in approximately eight minutes for a single experiment. The measurement data were analyzed using “spm99” software (The Wellcome Department of Cognitive Neurology, London). Figure 4 shows the average normalized neural activity obtained from 11 subjects (random effects analysis) in three experiments, superimposed on a standard brain model. The obtained results indicate that neural activity related to visual-form processes appears in the occipital/ventral occipito-temporal areas, while neural activity related to phonological processes appears in the left superior posterior temporal area (the so-called Wernicke’s area) and the left inferior frontal area (the so-called Broca’s area); additionally, the area of semantic processes may overlap the area of phonological processes.

Neural activity shown in Fig.4 had relatively low significance levels for nouns versus pseudo-characters, i.e., uncorrected probability, $p_u < 0.001$; for vowels versus pseudo-characters and pseudo-characters versus lines, $p_u < 0.01$ for demonstration purpose. Apart from these analyses, the number of voxels indicating significant signal changes was extracted and analyzed for each subject, using additional data obtained with character strings for pseudo-character and vowel tasks, these experiments and analyses confirmed that the indicated areas showed significant activity in relation to language processes. In particular, it is

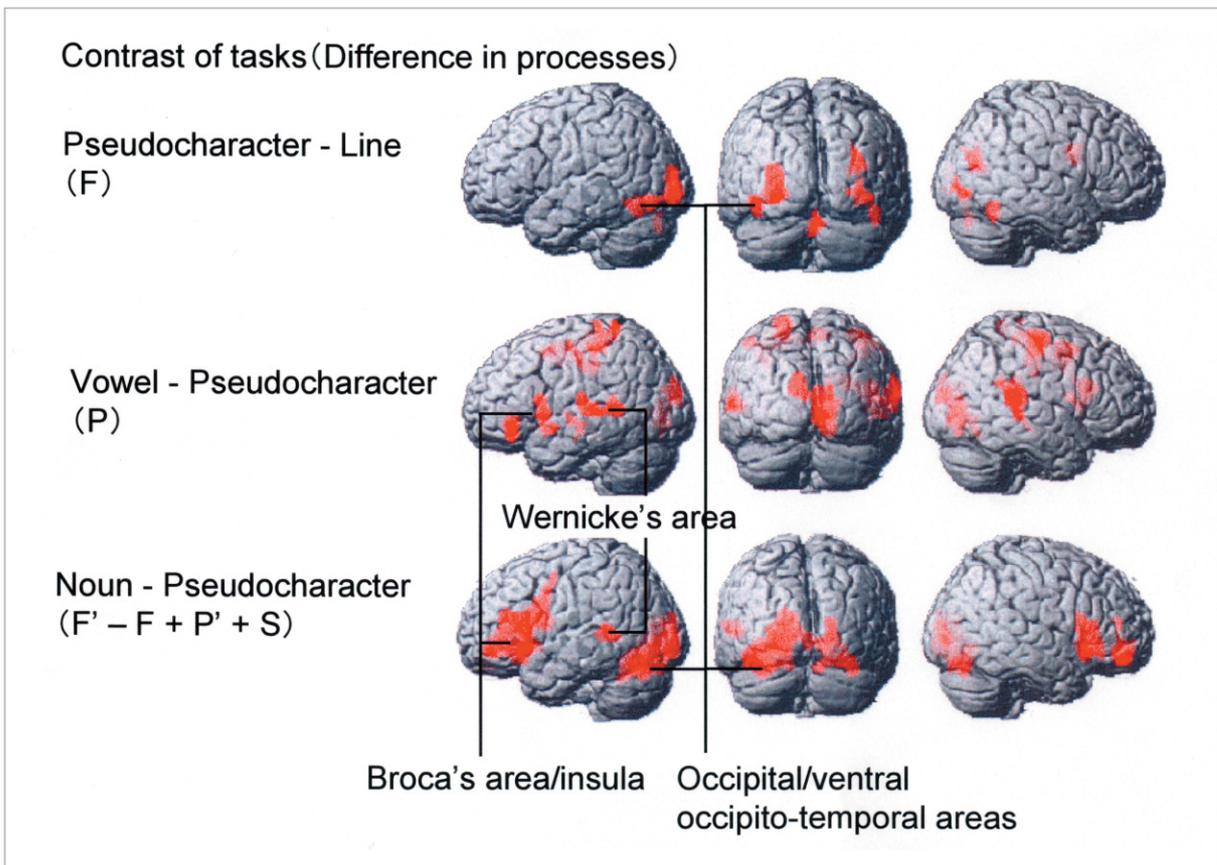


Fig.4 Neural activity during judgments of characters and words detected by fMRI

known that Wernicke's and Broca's areas are closely connected with aphasia, and that each of these areas participates in the comprehension and vocalization of speech. As for visual-form processes, detailed analysis revealed the following two points.

- (1) In the visual-form processes, neural activity showed no significant differences between processing of real katakana characters and pseudo-characters. In previous experiments using English alphabets, arguments arose as to the presence of a visual word-form center activated only by real words and pseudo-words. The present results indicated that no area appears dedicated solely to real katakana characters or katakana words.
- (2) When a single character was presented, no lateralization was observed in the occipital/ventral occipito-temporal areas. However, when two or more characters were presented, activity in the left hemisphere became greater than in the right hemi-

sphere. Based on various brain research (including lesion study of aphasia, electrical stimulus, the Wada method, etc.), it is known that most right-handed people perform major language processes in the left hemisphere (the dominant hemisphere for language). The present results indicated that although visual-form processes for a single character or for a single pseudo-character did not show lateralization, when processing a word consisting of two or more characters arranged in a line—or when processing an arrangement of pseudo-characters having a visual form resembling a word—left-lateralized activities peculiar to language processes were observed.

In terms of semantic processes, no new active areas apart from the area of phonological processes were detected; thus, it is very likely that the semantic area overlaps the area of phonological processes. This is supported by previous findings in which Wernicke's area

and the vicinity of the inferior frontal area were shown to participate in semantic processes. However, it must be noted that the other reports have indicated that a large number of areas participate in the semantic processes. For example, there are some reports that the left anterior temporal cortex (in which activity was observed in the present experiment—although in less than half of all subjects) was observed to participate in categorical processes and was therefore involved in semantic processes.

2.3 MEG measurement [2]

Our 148-channel whole-head MEG system (BTi, Magnes 2500WH) is shown in the right-hand portion of Fig. 3. There are a large number of neural cells in the brain, and for each group of processes a collection of these cells exchanges electrical signals to perform the various operations involved in information processing. The MEG is an instrument with highly sensitive superconducting magnetic sensors used to detect the magnetic field generated by a minute current flowing in neural cells. In our system, 148 sensors are arranged surrounding the head; these sensors measure the spatial distribution of the varying magnetic field. They measure the magnetic field generated by ion currents, or primary currents, which flow in the apical dendrite of pyramidal cells where these currents serve as input for the cells. When tens to hundreds of thousands of cells activate simultaneously in a regional area, a magnetic field is generated that is large enough to observe. Both EEG and MEG are used as methods of recording such electrical phenomena directly, and both feature temporal resolution on the order of ms, sufficient to record neural-cell activity.

However, EEG measures electrical potential on the scalp accompanying the return-current or secondary-current distribution which is generated by and in the vicinity of the above-mentioned primary current; as a result, EEG measurement is strongly affected by the distribution of conductivity in the brain. On the other hand, MEG measures the magnetic field

generated by the primary and secondary currents. Since the magnetic field generated by the primary current perpendicular to the cerebral surface is canceled out by the magnetic field generated by the secondary current and thus cannot be measured, MEG measures the magnetic field generated by the current flowing tangential to the cerebral surface. Therefore, MEG does not record the activity of the gyrus, but instead measures the neural activity around the sulcus.

In many systems, MEG is used to measure the magnetic field component perpendicular to the cerebral surface. Since only the primary current contributes to the perpendicular field component and the magnetic field penetrates brain matter without distortion (due to the brain's specific permeability of almost unity), it is believed that MEG provides higher spatial resolution than EEG. However, in light of each method's specific characteristics, EEG and MEG measurements may be viewed as complementary sources of information. Both are non-invasive methods of measuring neural activity from outside the head, and present no problems in terms of repeated experiments on a single subject. Note that unlike fMRI and PET, generally MEG is used not to record differences in the neural activity between tasks, but instead to measure overall neural activity relating to a task. With a single measurement alone, a response to stimuli provides only a weak signal relative to noise. Therefore, measurement of signals, e.g., during a few seconds for higher brain functions, is repeated 100 to 200 times; the resultant data are then averaged. Standard measurement conditions include a sampling frequency of 678 Hz and a frequency bandwidth of DC - 200 Hz. The measured signal is filtered with a digital band-pass filter (bandwidth: 0.1–40 Hz or 1–40 Hz) after measurement.

From the measured magnetic field distribution, the currents of a group of neural cells activating regionally in the brain are estimated in terms of a single current vector to model the source of activity in the brain. This current vector is referred to as an (equivalent current)

dipole. The magnitude of the dipole is a product of its current and length. The procedure of estimating a dipole from the measured magnetic field distribution is referred to as an inverse problem. Unfortunately, it is known that the inverse problem of finding a general current distribution does not have a mathematically unique solution, and thus various assumptions have been proposed to obtain a solution. The frequently used single-dipole approximation is based on the assumption that only one dipole is present; this enables us to find a solution by iterative calculation from the appropriate initial values. In terms of response to stimulus, it is often the case that this assumption is valid for the early component (up to approximately 100 ms). However, the single-dipole assumption sometimes fails for late components, as the neural activity spreads in the later stage. To evaluate the plausibility of this approximation in this experiment, several criteria were used, including a confidence volume of 4.2 cm³ or less for a significance level of 95%; degree of matching (or “goodness-of-fit”) between the meas-

ured magnetic field and the calculated magnetic field of 90% or more; and a relatively stationary dipole for 10 ms or more. Analysis methods for the multi-dipole inverse problem will be described later.

Figure 5 shows MEG waveforms measured with one subject for four of the tasks set forth in Fig. 2. Figure 6 shows an example of a dipole calculated with the single-dipole approximation superimposed on an MRI structural image. This example shows the analysis for the first large peak appearing in a noun-judgment (lexical decision) task, calculated using a magnetic-field distribution obtained using 38 sensors (each located within a red circle in the figure) and includes peaks of the magnetic fields directed outward and inward from the head. The dipole was found near the calcarine fissure, the area at which visual information first enters the cerebrum. This calculation was performed for the vicinity of each peak. Figure 7 shows the results together with the active areas obtained from the fMRI experiment and the processes related to the activity. Neural activity relating to the visual-

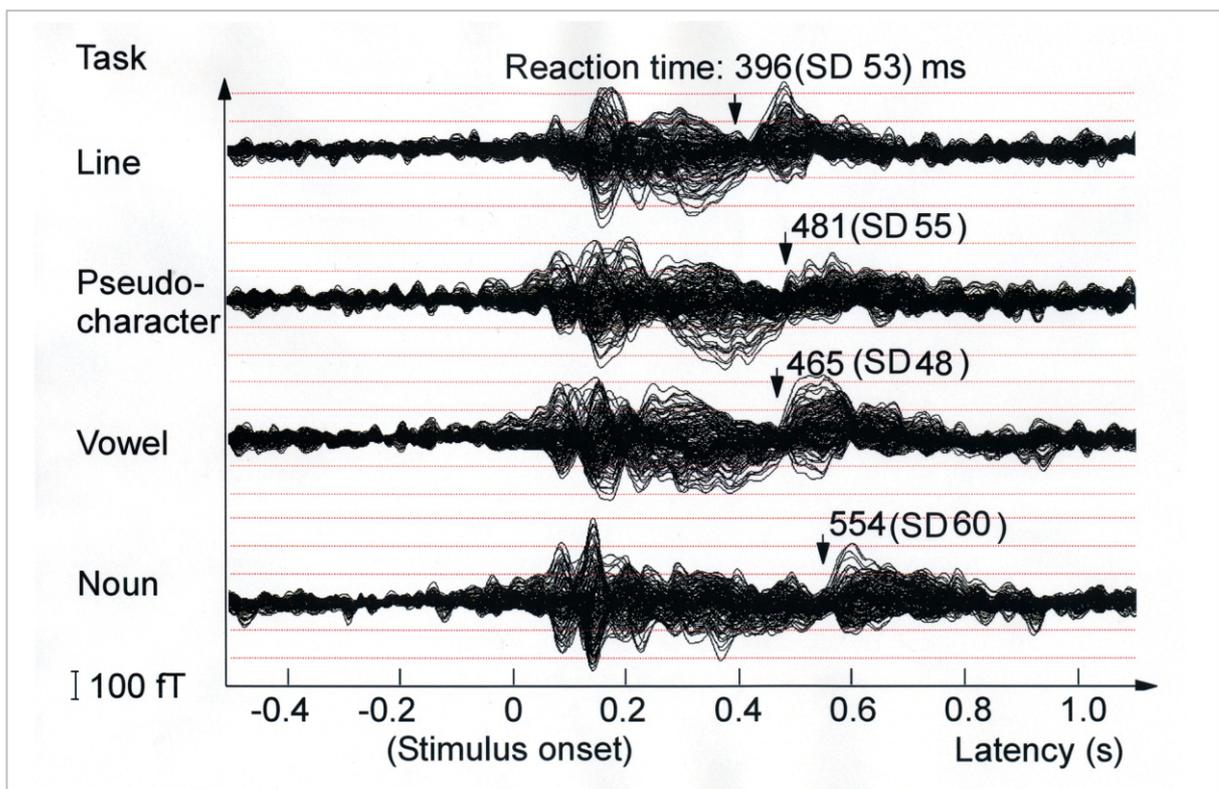


Fig.5 MEG waveforms for judgments of characters and words

form processes began in the occipital/ventral occipito-temporal areas approximately 100 ms after character presentation, while neural activity relating to phonological and semantic processes occurred 200 ms after character

presentation, in the left superior posterior temporal area (Wernicke's area), in the vicinity of the supramarginal gyrus, and in the left inferior frontal area (Broca's area or insula).

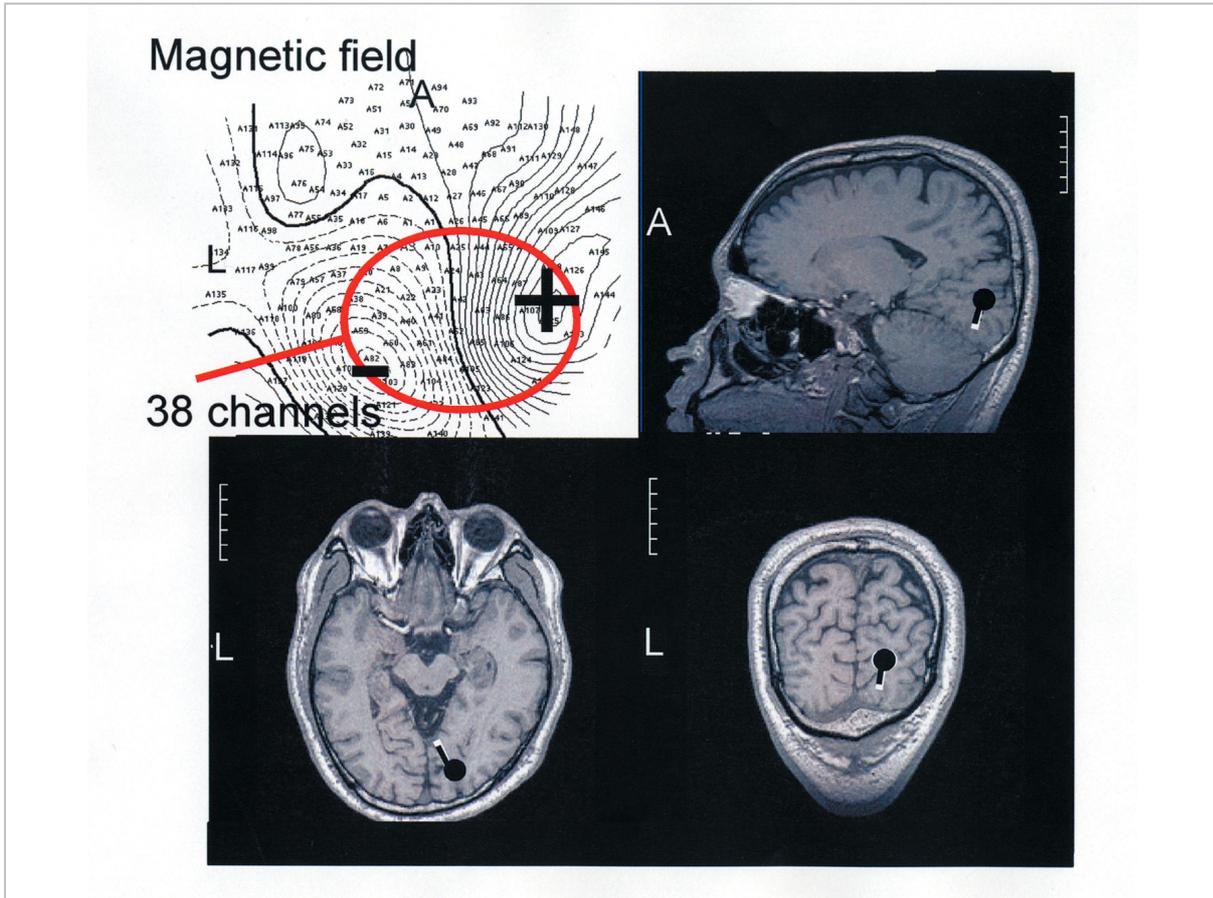


Fig.6 Magnetic-field distribution and dipole with latency of 100 ms for a noun-judgment task

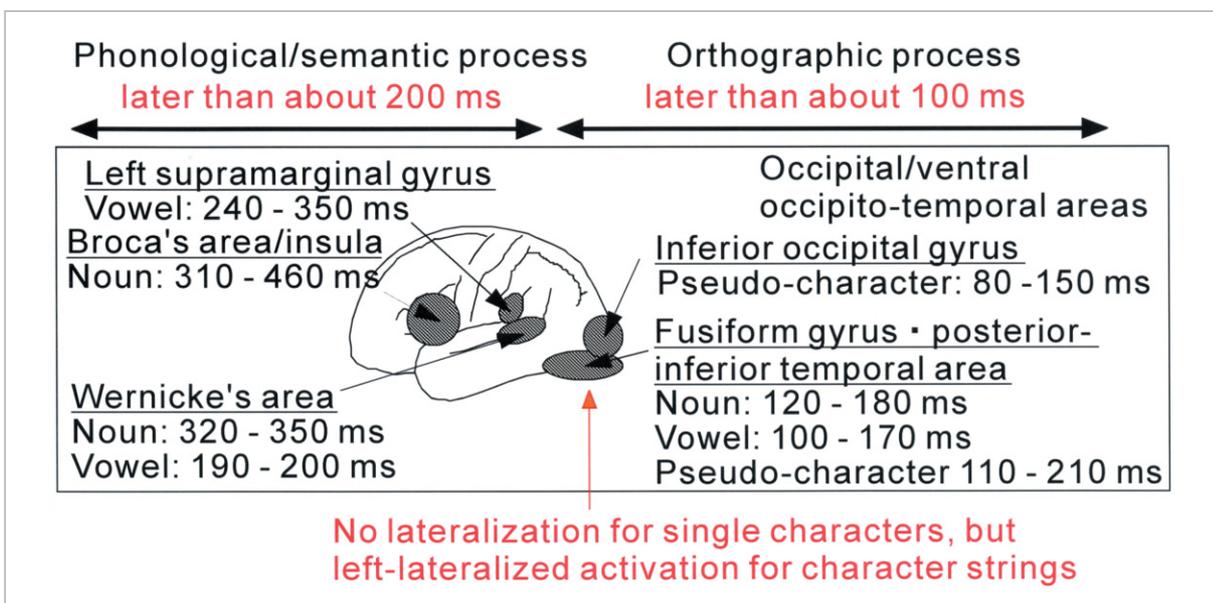


Fig.7 Summary of fMRI and MEG experimental results for characters and words

3 MEG dipole analysis method using fMRI

3.1 Comparison of active area detected by fMRI and by MEG (single-dipole approximation analysis) [3]

As described above, the fMRI and MEG measurement methods detect signals arising from entirely different mechanisms. That is, fMRI indirectly measures a change in blood flow incident to neural activity, making use of the BOLD effect; fMRI thus detects slow changes (within a period of a few seconds or more) which is limited by hemodynamic delay. On the other hand, MEG directly measures the electrical activity of the neural cell as a magnetic field, and is capable of measuring only the component of a current that is tangential to the cerebral surface. Comparison of the results of the two methods is not easy. However, for the early MEG component evoked by stimuli, it is possible to compare the dipole location obtained by single-dipole approximation with the location of fMRI activity.

Figure 8 shows an example of this comparison for the dipole of a 20-ms component with electrical stimulus of the finger. Sixteen sets of sample data were obtained for different subjects, different fingers, and different hands (right and left). With fMRI, the neural activity appeared in Brodmann areas 3b, 1, and 2. When dipole locations determined by MEG were compared with area 3b, to which much of the somatosensory information from the thalamus was projected, eight cases were observed in which the dipole location fell within the fMRI active region; in the remaining eight cases in which dipole locations fell outside this region, the average difference between the dipole locations and the fMRI active region in area 3b was eight mm, with a standard deviation (SD) of 4 mm (Fig. 8). However, since this difference was comparable to an evaluated error arising from each measurement method and from a superposition of coordinates of MEG and fMRI—as much as 6 mm, it was judged that no signifi-

cant difference could be detected in terms of location between MEG and fMRI measurement of the early component of somatosensory stimulus.

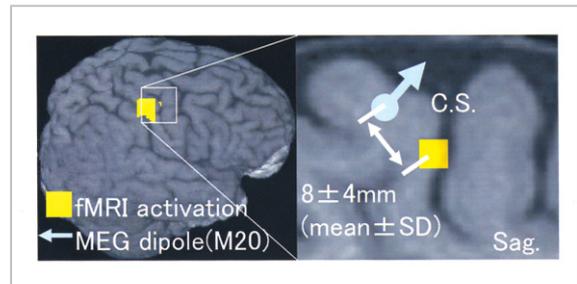


Fig. 8 Dipole obtained from MEG data and location of fMRI activity for electrical stimulus of fingers

There is no precise method for comparing the neural activity detected by fMRI and MEG, in response to other stimuli and the activities reflecting higher brain functions (e.g., late-stage components). It is necessary to verify the reliability of all measured data; for example, by verifying reproducibility among subjects and comparing detected neural activity with the results of previous brain research. There is one example in which different measurement results were obtained between the two methods. In one block-design experiment a somatosensory or auditory stimulus was presented at a rate of repetition of once every two seconds while subjects passively perceived it. With MEG, a clear waveform was obtained by averaging approximately 100 data. With fMRI, neural activity in the somatosensory area or auditory area was difficult to obtain, but neural activity became apparent if the rate of repetition of the stimulus was increased. The reason for this phenomenon is that with fMRI, the signal value decreases when activity occurs during short periods at a low rate of repetition; this decrease is due to the integrative effect of the hemodynamic delay. Moreover, neural activity under control conditions disappears by subtracting neural activity under the control condition from that under the test condition. Thus, these examples show that there are some cases for which the source of activity

contributing to MEG cannot be observed using fMRI; this case is referred to as the “fMRI-invisible dipole.” On the other hand, there are other cases where fMRI detects neural activity, but this activity does not contribute to MEG. This phenomenon can be attributable to one of several causes: MEG fails to detect the activity of the gyrus; a filter blocks some frequency components; or a component not synchronized with the stimulus becomes undetectable when the evoked responses are averaged.

3.2 MEG dipole analysis method constrained with location information determined by fMRI (fMRI-constrained multi-dipole estimation method) [4]

fMRI has a good spatial resolution. For example, a 1.5-T system can provide a spatial distribution of neural activity in voxel units from 3 to 4 mm. Here, the spatial filter used to suppress noise reduces the spatial resolution. Typically, even with multiple neural

activities, fMRI identifies each activity location with spatial resolution of a few millimeters. On the other hand, as described above, it is impossible to uniquely find a multi-dipole solution based only on MEG data. One promising solution to this problem involves an attempt to determine a multi-dipole solution using active location data obtained by fMRI.

The method based on this idea would enable us to analyze neural activity with high reliability, meaning that activity related to the late components (reflecting higher brain functions such as language) is obtainable without artificial mathematical assumptions. The method that we have developed based on this concept involves dividing the active volumes detected by fMRI into sub-volumes of approximately 2 cm, placing a dipole within every sub-volume, fixing the locations, and determining the magnitude and direction of the dipole moment based on MEG temporal information (Fig. 9). The size of the above-mentioned division is determined based upon a large number of simulations in which the

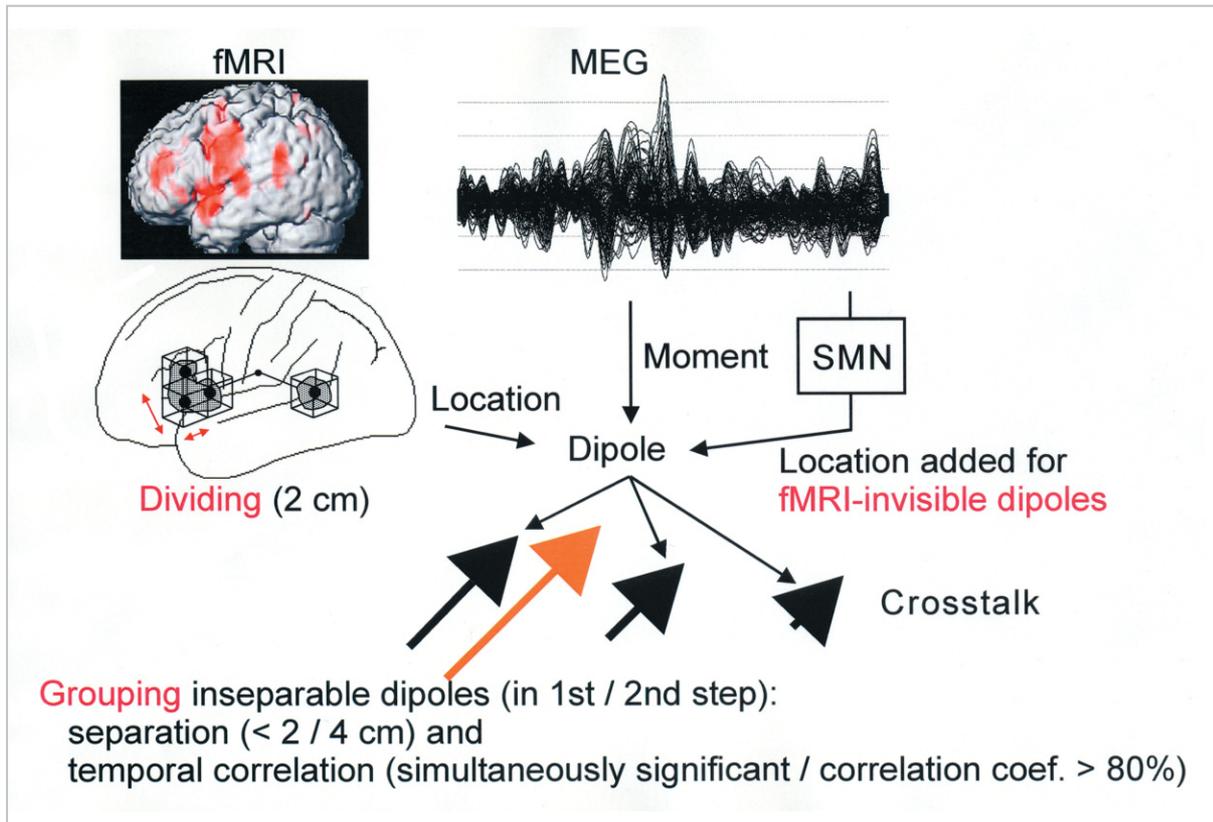


Fig.9 Method of estimating fMRI-constrained multiple-dipoles

measured magnetic field (MEG) is successfully explained by the dipoles (correlation between the measured magnetic field and the calculated magnetic field is 94% on average). With this method of division, up to approximately several dozen dipoles may be reached in typical neural activity detected by fMRI for a language task. If the number of unknown parameters (i.e., twice the number of dipoles, since for a single dipole, the current of tangential components features two degrees of freedom), is equal to or less than the number of MEG sensors (in our case, 148), a unique solution can be obtained without further restrictions.

However, since the dipoles are placed discretely, generally a discrepancy appears between the dipole location and the true location of the source of neural activity. As a result, if fitting of the dipole moment is performed by minimizing the sum of the squares of differences between the calculated and measured magnetic fields, the moments of neighboring dipoles have finite values. This phenomenon is referred to as “crosstalk.” A large number of simulations of fitting dipoles, in which the locations and moment orientations of the dipoles and sources were varied, have revealed a high probability that other dipoles within a few centimeters of the principal dipole (in the case in which dipoles are placed at divisional units of approximately 2 cm) are subject to significant crosstalk, depending on their specific locations and moment directions. Therefore, we devised two steps of separation threshold; within 2 cm and within 4 cm, when the neighboring dipoles have a high temporal correlation, these dipoles are judged to be indistinguishable, and a vector-sum of the moments is taken. This is referred to as grouping. In this way, spatial resolution for the present method becomes approximately several centimeters. Although this is inferior to the single-dipole approximation in terms of spatial resolution (if the signal-to-noise ratio is equal to 3 or more, error under the single-dipole approximation method is on the order of several millimeters), a solu-

tion can be obtained for multiple dipoles relying on fMRI alone (and not, for example, by relying on frequently used mathematical assumptions on current norm). As a result this method can be said to provide highly reliable solutions.

The above-mentioned method does not place any dipole in an area in which fMRI cannot detect neural activity, and thus fails to find an fMRI-invisible dipole. In order to compensate for this issue, this method is used together with the Selective Minimum Norm (SMN) method, proposed by Professor Okabe of the University of Tokyo. SMN is a multi-dipole inverse solution in which the head is segmented in a mesh at a certain interval (e.g., 1 cm), and seeks a solution that minimizes the first-order current norm on the condition that a number of mesh points or the number of dipoles is equal to that obtainable from measured data items. Any dipole below the noise level is discarded. If a solution dipole obtained by SMN is located 2 cm or more from any dipole locations determined by fMRI, this dipole is judged an fMRI-invisible dipole and its location is added to the group of solution dipoles. The moments of all dipoles (usually from 40 to 60) are then fitted to the measured magnetic field (Fig. 9). If an fMRI-invisible dipole was overlooked by SMN and no dipole is placed in its vicinity, significant crosstalk may take place in the remote dipoles. However, if such a large difference in location occurs, the method does not provide an erroneous solution, but instead reveals that no significant solution is available. This is realized by the fact that when determining the significance of a dipole, the method stipulates that the dipole must be significant relative to noise, that excellent correlation should be obtained between the measured magnetic field and the calculated magnetic field (94% or more), and that the contribution ratio of the magnetic field should not be too low ($> 20\%$).

Several other methods of solving the MEG multi-dipole problem have been proposed. In one, dipoles are placed at the mesh points of the cortical surface that includes pyramidal

cells in the gray matter, and several thousand dipole moments are solved using mathematical assumptions such as the minimum norm. In another, the moments are obtained by Wiener estimation, with priors given by fMRI data for dipoles fixed at several to tens of thousands of mesh points. With the latter method, a problem has been raised: with an fMRI-invisible dipole, the selection of prior values may result in significant variation in the obtained solution [5].

Figure 10 shows one example of a solution obtained by applying our fMRI-constrained dipole analysis method to the lexical decision data introduced in Chapter 2. A red frame indicates a latency range, where moment magnitude was significantly larger than the noise level and the contribution ratio was not too low (i.e., significant activity was detected). The activity of the occipital/ventral occipito-temporal areas began at about 100 ms, and activity near both Wernicke's and Broca's areas was seen at 200 ms and later, which was consistent with the solution obtained by sin-

gle-dipole approximation. Although activity in the occipital/ventral occipito-temporal areas was obtained only for up to 200 ms by the single-dipole approximation, according to this multi-dipole analysis, this activity was found to continue for quite some time in the later stage [6]. A paper on this phenomenon is currently being submitted.

3.3 Application 1 — inner speech experiment [7]

In this section we will describe an example in which the analysis method set forth above is applied to data relating to the neural activity of inner speech (speech that is not pronounced vocally but is instead internally formulated). The previous section describes neural activity during a lexical decision task which included phonological processes. The processes include phonological transformation of viewed characters, phonological analysis of the vowel [a], and inner speech accompanying these tasks. In an attempt to separate these processes, an experiment was conducted to

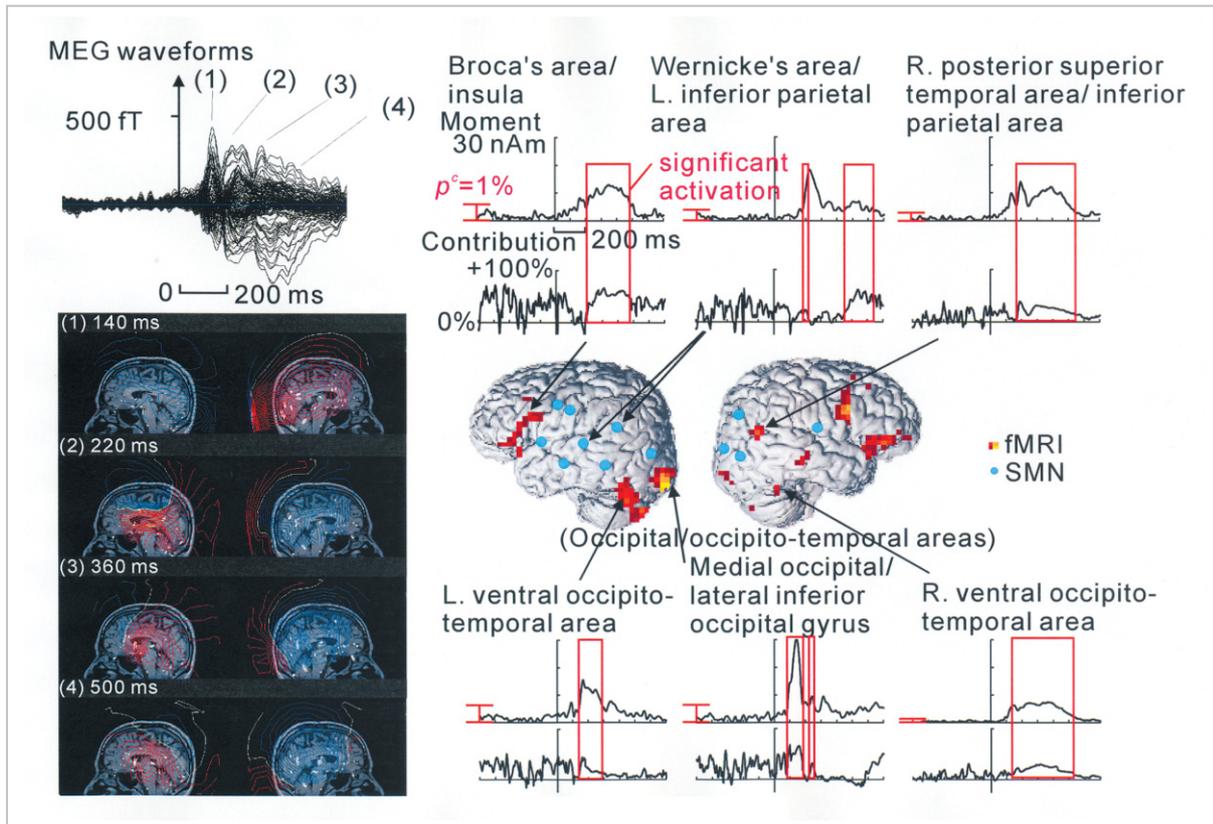


Fig. 10 Neural activity during lexical decision estimated by the fMRI-constrained dipole method

measure the neural activity accompanying inner speech (Fig. 11). We used Sternberg paradigm, a delayed-matching task which was originally used as a short-term memory task. More specifically, in this task a subject executed the following three processes sequentially: three to six characters presented in series were committed to memory (memorization); the memory is maintained by rehearsal (inner speech); and finally, after a character was presented, a judgment was made as to whether that character was included in the memorized character string, with the subject's answer provided by pressing a button (matching judgment). In this experiment, the neural activity of the inner speech process during rehearsal was measured. Since the trigger, or time at which the inner speech process was initiated, was required for MEG measurement, a prompt was given three times during the rehearsal period, and the subject was asked to execute inner speech each time he/she saw the prompt. The neural activity detected by fMRI relating to three processes cannot be separated unless the respective periods are of sufficient length as compared with hemodynamic delay; this would require experimentation of relatively long duration. Therefore, in most previous experiments with this task, the three processes were not separated, and the relation between the processes and measured activity was analyzed by comparison between different conditions involving varied processing load, e.g., with varying numbers of characters to be memorized. Notwithstanding the challenges described above, the use of MEG—with its high temporal resolution—eliminates the need to lengthen the processes.

fMRI and MEG measurements were conducted with this task. The control conditions of fMRI were such that pseudo-characters were presented instead of katakana characters to prevent memorization; rehearsal (inner speech) was not performed; and in the matching judgment period the subject was asked to press a button immediately after the pseudo-characters appeared. Figure 12 shows the results analyzed by the fMRI-constrained

dipole method for a single subject. In this example, no significant dipole group appeared in the left hemisphere, and activity was observed in several areas in the right hemisphere. This result with inner speech is contrary to that with the lexical decision where activity appeared in the left hemisphere (the language-dominant hemisphere). In the present inner speech experiment, neither phonological transformation nor phonological analysis took place in the rehearsal period; only inner speech was requested. Additionally, inner speech in this case involved a meaningless character string and was repeated three times, prompted by cues. Thus it was probable that prosody processes such as pitch and rhythm were mainly performed with minimal phonemic process. In this respect, previous reports have indicated observation of neural activity in the right hemisphere using the tasks relating to pitch, rhythm, and music. The current interpretation is consistent with these findings.

3.4 Application 2 — visual search experiments [8][9]

When we read and attempt to understand sentences, we execute visual-form processes for characters and words, and distinguish words from their background. Moreover, as is shown in cases of attentional dyslexia, in which single words may be read but some words are exchanged between adjacent lines when multiple words are presented, spatial attention is also required during reading. However, we did not yet know precisely where and when in the human brain visual-form processing of words takes place, particularly when multiple processes including attention and information extraction are performed. Thus in order to clarify the neural activity required to extract a word from a sentence, we conducted a detection experiment involving a very simple line and analyzed the data with the above-mentioned multi-dipole analysis. We found that the calcarine fissure (an area involved in feature extraction) and its adjacent areas activated approximately 100 ms after

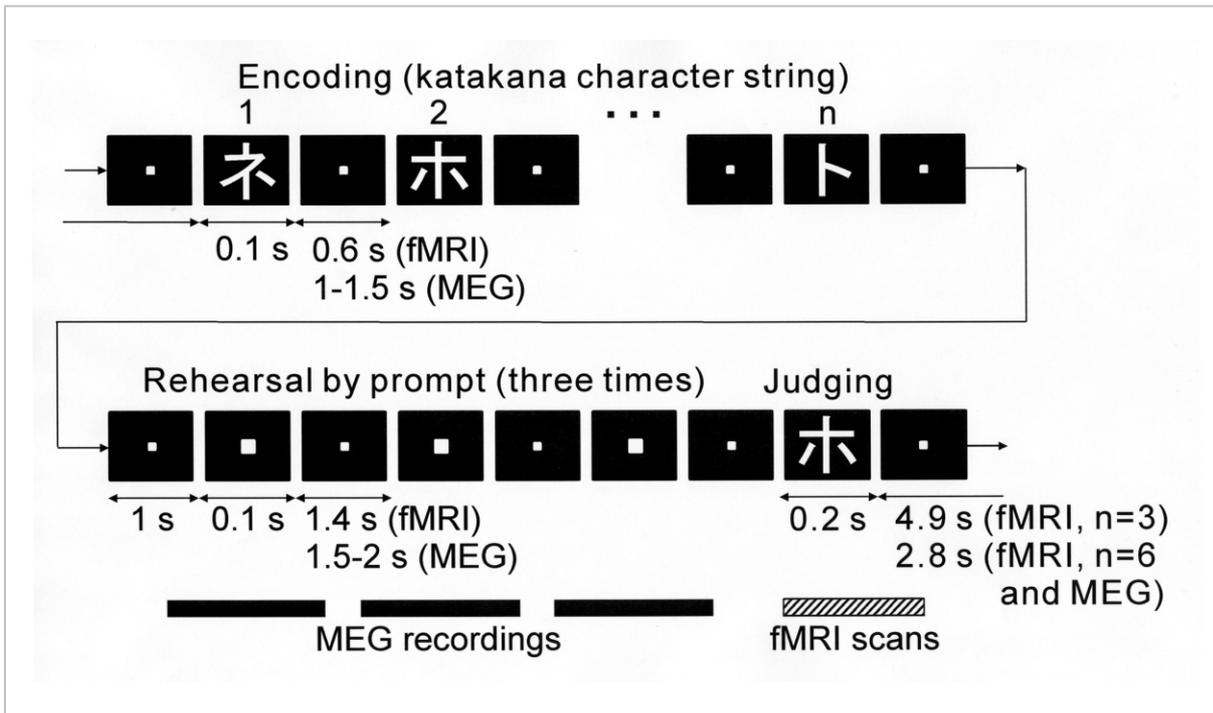


Fig. 11 Stimulus in the inner speech experiment

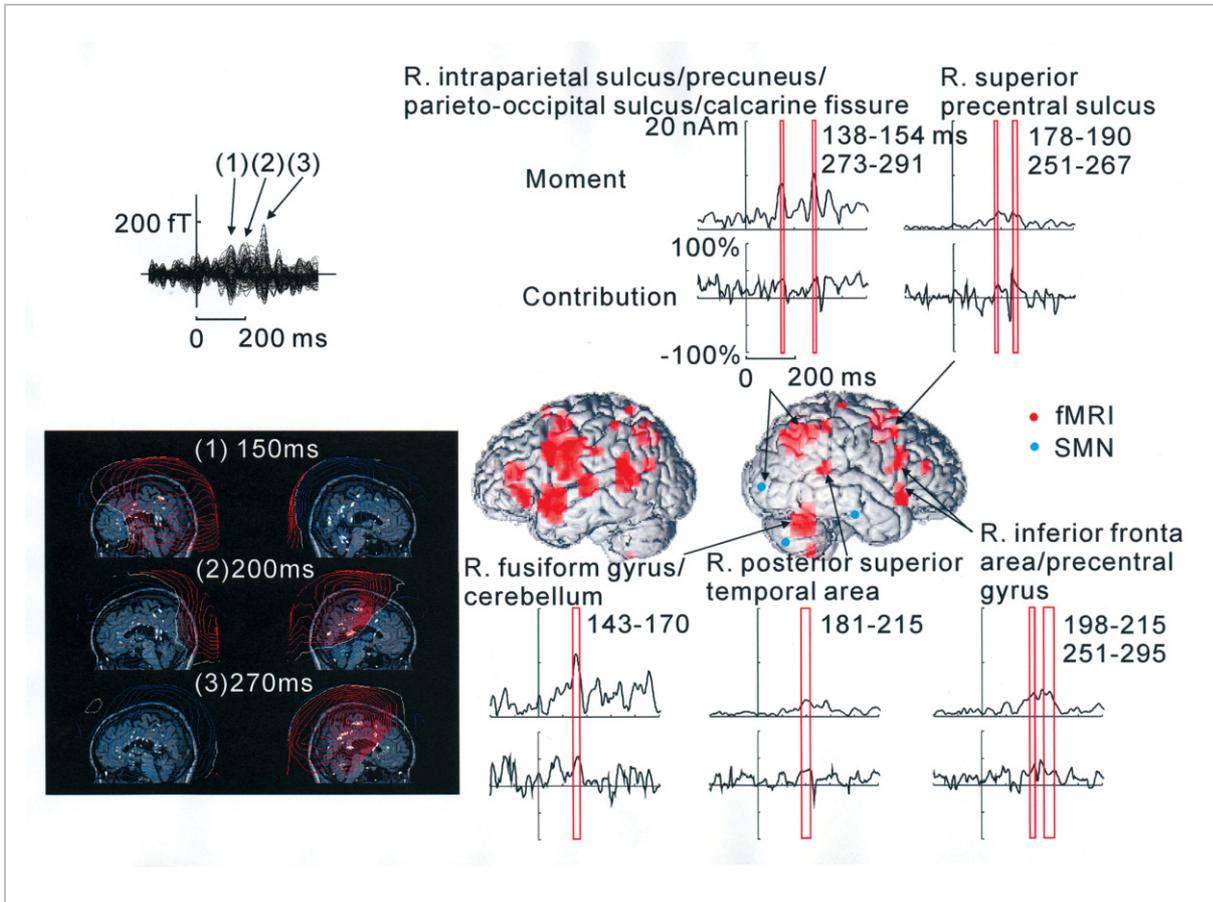


Fig. 12 fMRI-constrained dipole estimation of neural activity by an inner speech task

stimulus (Fig. 13 A), and that the fusiform gyrus (an area involved in visual-form processing) and its vicinity activated approximately 15 ms later (Fig. 13 B). The calcarine fissure then activated again approximately 100 ms following the initial activity. We observed that the superior temporal sulcus and the intraparietal sulcus, which are related to the segmentation of visual items as well as to spatial attention, activated just after the initial activity in the visual areas, whereas this activity was enhanced when information was present to be extracted from the visual stimuli. When the intraparietal sulci of the right and left hemispheres were compared, it also became clear that activity was dominant in the right intraparietal sulcus. The processes involved in distinguishing a specific visual item from a background are not specific to vision, in terms of extraction of information, but are common to other sensory modalities. It has been remarked that the other processes peculiar to language, such as the process of the semantic relationship between foreground and background elements, would take place in the reading of sentences. We intend to develop this study into research on the processing of words in sen-

tences presented visually. Accordingly, if we are to understand the processing system within the human brain, it is indispensable that we clarify the active times of multiple cerebral areas as well as the sequence of neural activity. Multi-dipole analysis is considered to have opened a path toward such clarification.

4 Neural activity during sentence processing [10]

Syntactic processes take place during sentence processing in addition to lexical processes for words. There were previous reports in which activation for these processes were separated. Unlike those, we conducted an experiment involving a task in which the vertically presented characters of the novel “Kokoro (Heart)” by Soseki Natsume were read normally. Although it was difficult to separate neural activity into parts corresponding to respective groups of processes in this experiment, it was possible to measure the overall neural activity corresponding to the language processes involved in the natural reading of sentences. We investigated how neural activity changed when the reading speed, i.e., the

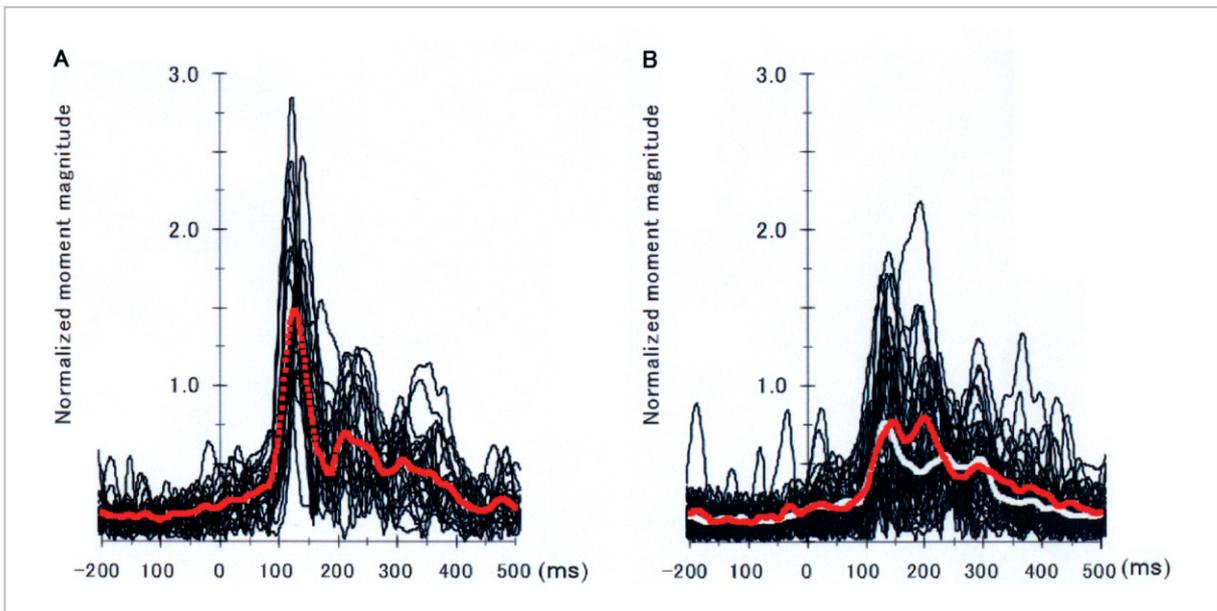


Fig. 13 Neural activity in the visual areas (A) and near the intraparietal sulci (B) clarified by fMRI-constrained dipole estimation ($n=24$). Black lines denote activity for each subject, and a red line denotes the average activity across subjects in the visual areas for (A), while a red and white line denotes the average activity in the right and left intraparietal sulcus respectively for (B).

processing load, was varied. Neural activities—associated with normal reading speed and rapid reading speed, respectively—were measured for four subjects who had received training in rapid reading and for four subjects who had not received such training. An ordinary person reads approximately several words per second, while the trained rapid readers can read two orders of magnitude faster than normal readers (one second per two-page spread of a standard paperback) while still understanding the content. We were thus able to measure the dependence of neural activity across an extremely wide range of reading speeds.

With tasks in which subjects are asked to read characters presented on a wide visual field, significant eye movement occurs. Consequently, MEG data would be superimposed with large artifacts—magnetic fields caused by phenomena other than the experimentally targeted neural activity—rendering measurement of this neural activity difficult. Thus, target activity in this experiment was meas-

ured using fMRI. A block-design experiment was conducted; in the test conditions subjects read the text of a novel, and in the control conditions characters were replaced with pseudo-characters where subjects were asked to move the eye along them as in the test condition. The two conditions were alternated approximately every 40 seconds. Figure 14 shows the measurement results for one rapid reader. In this example, neural activity around Wernicke’s area decreased for rapid reading. Summarizing the data for all subjects, neural activity tended to decrease in language areas, i.e., Wernicke’s and Broca’s areas, when readers executed extremely rapid reading.

A previous report had indicated that, for word processing at rates near one word per second, as the rate of word presentation increased, neural activity also increased. The present experiment showed that on the contrary, at reading speeds one or two orders of magnitude faster than the ordinary speed, neural activity decreased. As Wernicke’s and Broca’s areas are related to phonological

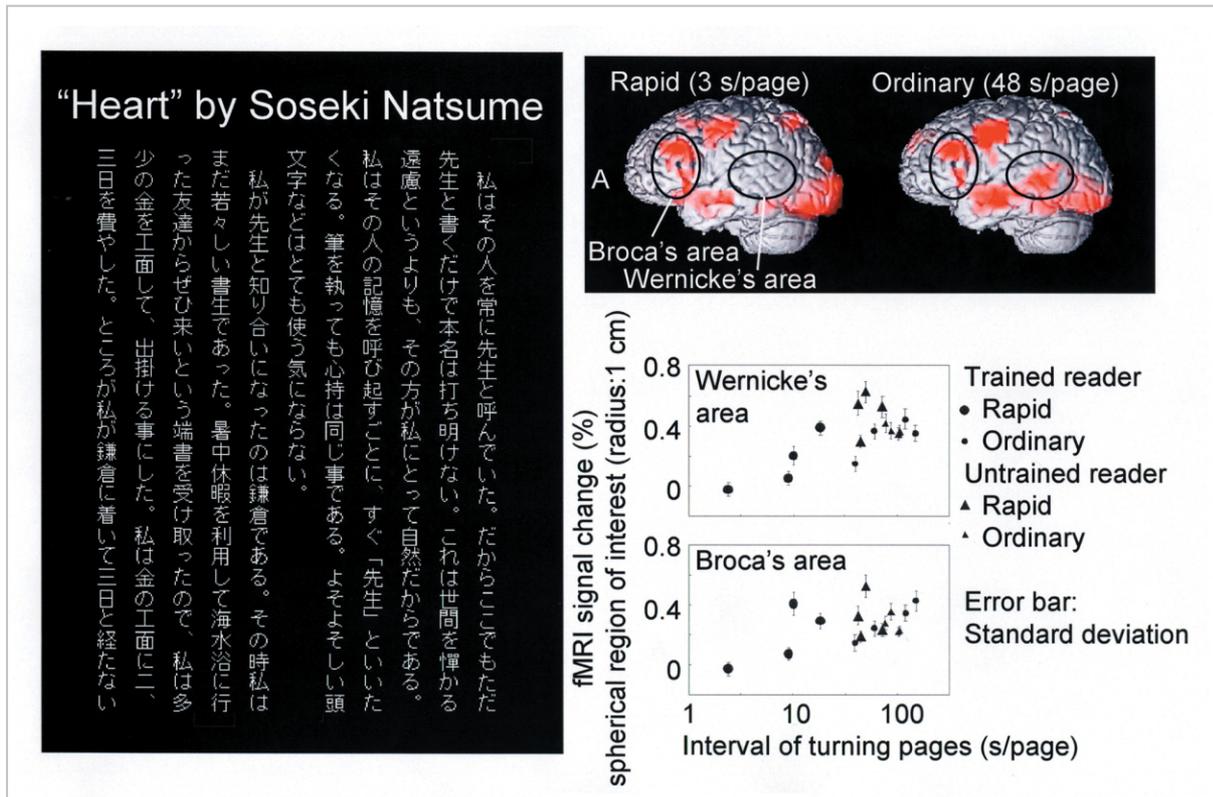


Fig. 14 Sentence-reading task, neural activity of a rapid reader, dependence of neural activity in the language areas on reading speed

processes, the results of this experiment point to the possibility that a subject may execute rapid reading by omitting the inner speech processes. However, other reports have indicated that these two areas participate in semantic and syntactic processes as well, and so it is also possible that the current results reflect a reduction in these processes.

It is known that a rapid reader reduces eye movement in the vertical direction along sentence columns and moves the eye nearly horizontally when rapidly reading such sentences. Reduction in vertical eye movement and in neural activity observed in the present experiment indicates that the rapid reader acquired a strategy of rapid reading by reducing these processes through training. However, there is no clear index to determine the degree of comprehension during rapid reading, i.e., to assess quantitatively the semantic and syntactic processes; this issue thus remains as a future subject of investigation.

5 Language priming experiments

Current research in our group has led to formulation of an experiment in which two words are presented, having started from the lexical decision experiment described above—experiment for subsequent single-word processing. This experiment is designed to observe how processing of a single word (the “target”) is affected by the processing of a word presented before the target (the “prime”). This design may offer a link between single-word experiments and those involving sentences in which multiple words are arranged in a line. Moreover, it is anticipated that the data obtained by observing the relationship between the processing of the two words will be useful in modeling the brain’s linguistic mechanisms. With this in mind, we began experiments in which the lexical relationship between prime and target was modified, or in which the time interval between presentation of the two words was varied. The latest results of these experiments are described below.

5.1 Semantic priming [11]

Visual presentation of a word is frequently used to study the priming effect. It is known that a preceding word (prime) having a semantic relation with a subsequent word (target) facilitates categorical judgments of the latter. This phenomenon is referred to as the semantic context effect. However, the brain region and sequence of the language processes producing this effect have yet to be clarified. In our experiments, katakana words under the control of the number of characters, familiarity, and plausibility, were extracted from an NTT database, and MEGs were compared between cases where primes and targets were semantically related and where they were not. The subject was asked to judge whether a target word presented in the left visual field belonged to a previously instructed category and to press a corresponding button (Fig. 15). When the target word was semantically related to the category, neural activity increased near the fusiform gyrus located in the right occipital areas, which is related to visual-form processing ($p < 0.01$) approximately 140 ms after the presentation of a target word; at 300 to 400 ms after the presentation, activity increased in the left temporal areas, i.e., in the language dominant hemisphere ($p < 0.03$). Moreover, when a first-order regression line was evaluated from magnetic field strength before target presentation, this field strength was shown to have increased in these regions before the target presentation. These results showed that, in terms of connectionist models, once prime word processes were performed, a node representing the prime word activated, nodes of the other words that were included in the category of the prime word automatically activated, a semantically relevant target was then input, and thus the activity associated with the prime facilitated the activity for the target related to visual-form and semantic processing. Going forward, we are aiming at developing a model of language processes that will incorporate a delay element, a time constant, and an excitatory or inhibitory nature of the processing in neural activity in these cere-

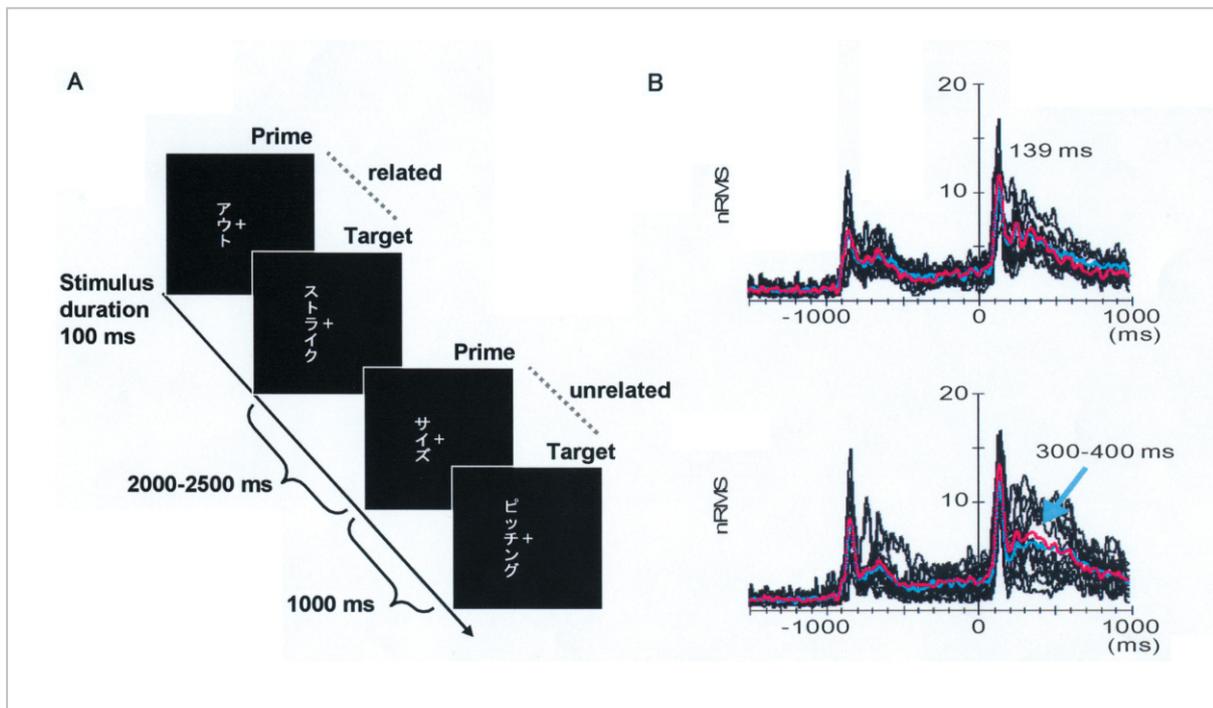


Fig. 15 Semantic context effect: (A) examples of experimental tasks where subjects judged whether target words belonged to category "baseball", and (B) normalized root-mean-square values of magnetic fields in the right occipital area (upper) and left temporal area (lower). Red and blue lines denote the waveforms averaged across subjects ($n=8$) for the conditions that prime words were semantically related or unrelated to target words respectively.

bral areas.

5.2 Repetition masked priming [12]

An experiment with a "masked priming paradigm" was performed in which a mask, a prime, and a target were alternately shown where the time interval between the prime and the target was very short (Fig. 16). Since the prime presented during a short period fell between the mask and the target—which generate, respectively, forward and backward masking effects—the subject is not conscious of the content of the prime, nevertheless this content affects processing of the target.

This paradigm has been used to investigate instances of automatic processing. The subject was asked to judge whether or not a target katakana word belongs to a previously instructed category and to respond by pressing a button. We measured MEG for two conditions: in one, the prime word was the same as the target, but represented in hiragana, unlike the target (with the prime); in the other it was replaced by a pseudo-character string (without

the prime). Since the stimulus was not presented against a blank background but presented such that the stimulus alternated among mask, prime, and target, the MEG component relating to early visual-form processes was small. Rather the MEG component reflects higher visual-form and lexical processing (the latter involving phonology, semantics, etc.).

Our latest MEG experiments revealed an example in which a test condition (with a prime) resulted in a faster response time than a control condition (without a prime); additionally, neural activity in the later stage (> 350 ms) was greater with the prime. In terms of modeling neural activity related to language processes, a connectionist model was proposed in which a node was provided for each group of processes and its neural activity propagated from node to node that were related to the processes (linear combination). Comparing the presence or absence of a prime using this model, when the prime is present, the lexicon is activated by the prime; as a result activity related to the subsequent pres-

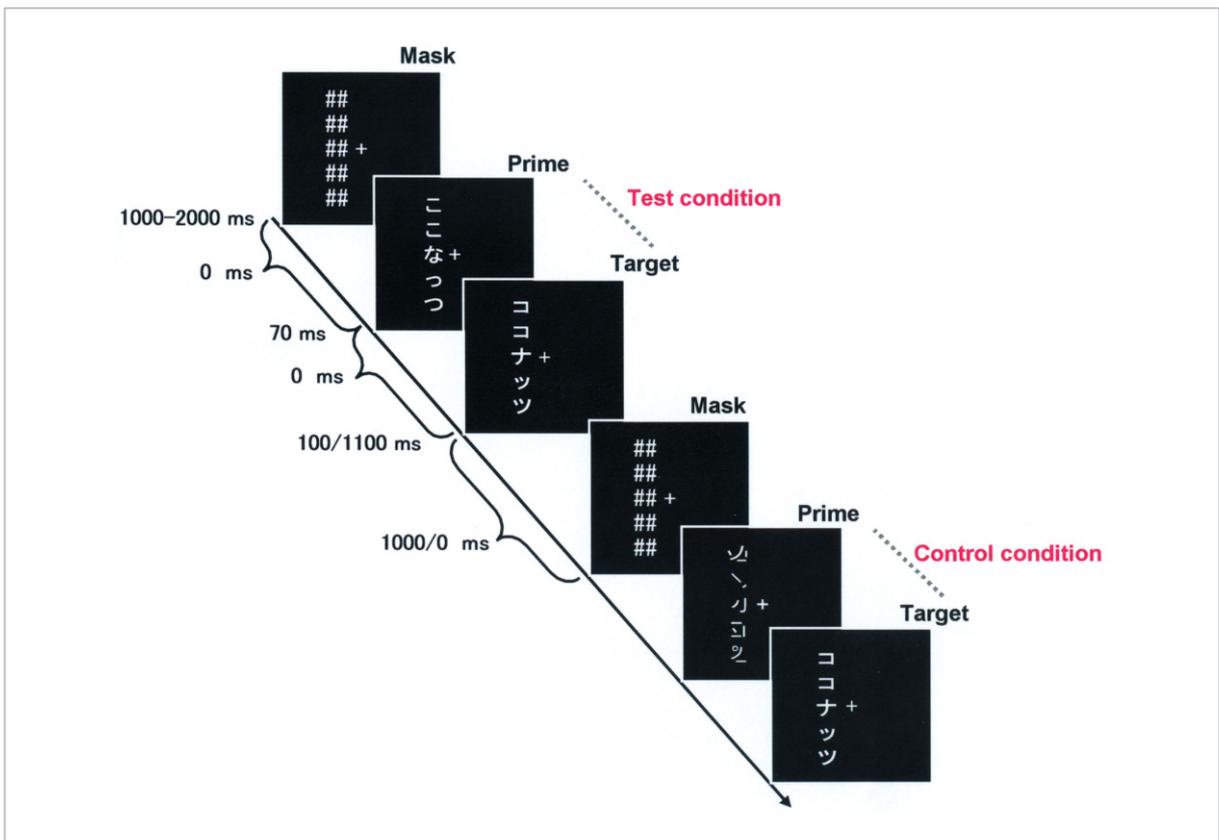


Fig. 16 Examples of stimuli for repetition masked-priming experiment, where subjects judged whether target words belonged to category "foods".

entation of the target takes place earlier and is larger; these factors thus enable a qualitative explanation of the reduced response time and increased neural activity (Fig. 17). Note that in this example, since only an excitatory connection, but no inhibitory connection is considered, detailed investigation and experimental verification remain to be performed.

To enable detailed analysis of the waveforms obtained in this sort of priming experiment, a new signal-processing method has been proposed [13], and research to explore the origin of the waveform component [14] is underway.

6 Conclusions

We introduced our studies of measuring the neural activity of language processes using fMRI, and MEG in order to clarify the language-processing mechanism in the human brain. The language function, unique to humans, includes a number of features that

cannot be investigated by animal experiments, and thus non-invasive measurements of cerebral functions are particularly important. We have developed a highly reliable method of analyzing multiple neural sources of activity by combining fMRI, which excels in spatial resolution, and MEG data, which provides precise temporal resolution.

Using these methods of measurement and analysis, we analyzed the cerebral areas and relevant activation times participating in visual-form, phonological, and semantic processes on the word level. It was found that visual-form processes started approximately 100 ms after character presentation near the occipital/ventral occipito-temporal areas, while the phonological and semantic processes began 200 ms or more later in the left superior posterior temporal area, i.e., in the vicinity of Wernicke's area, and in the left inferior frontal area, i.e., in the vicinity of Broca's area. The visual-form processes for real katakana characters and those for pseudo-characters did not

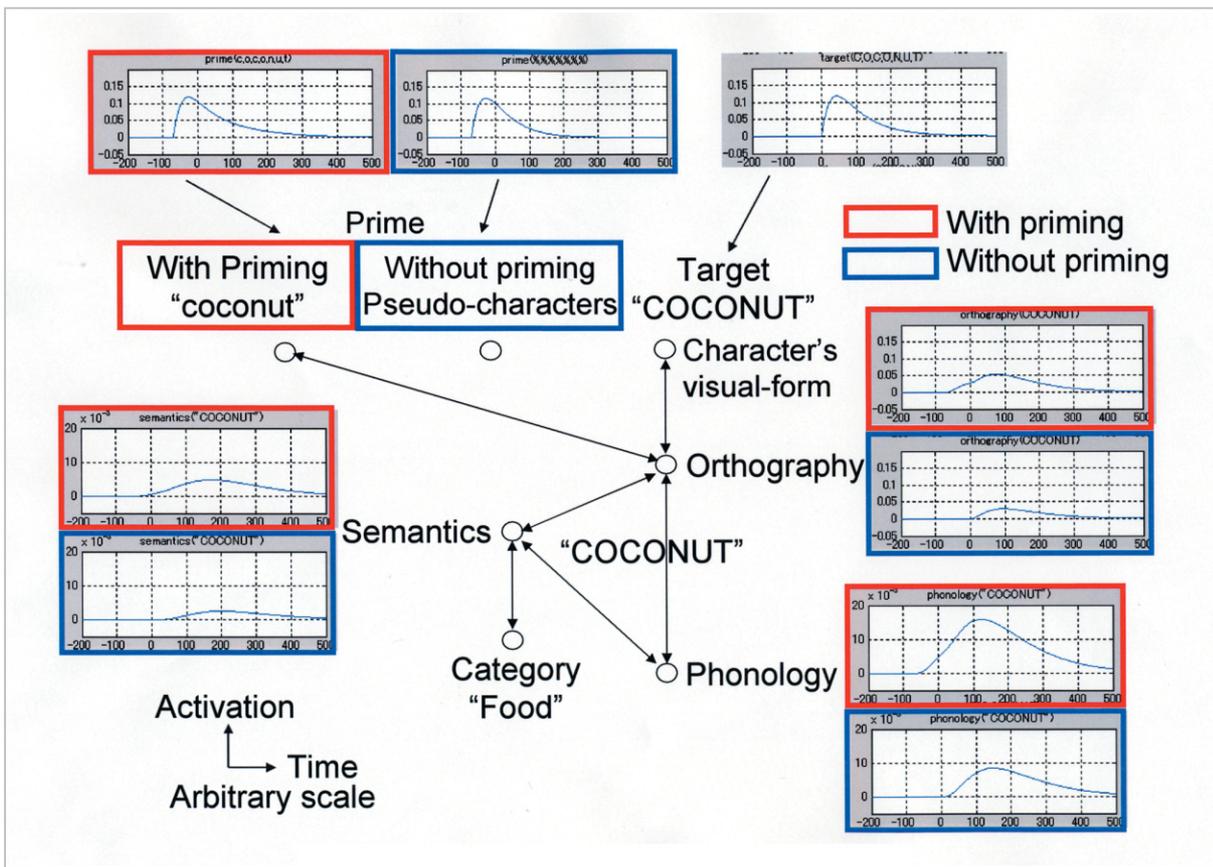


Fig. 17 Connectionist model of lexical processes

reveal a significant difference in terms of neural activity, and word-level processes generated an augmented activity distribution in the left hemisphere, which is characteristic of the language processes. In addition, in terms of inner speech of meaningless character strings prompted by cues, neural activity was observed in the right hemisphere, which is considered to reflect prosody processes.

Further, we clarified through visual-search experiments using single line stimuli that neural activity related to the earlier processes began approximately 100 ms after stimuli in the occipital areas (near the calcarine fissure). Fifteen ms later, visual-form processes took place in the ventral occipito-temporal areas (near the fusiform gyrus), and neural activity related to the process of separating a visual item from its background, as well as activity related to spatial attention occurred in the vicinity of the superior temporal sulcus and in the vicinity of the intraparietal sulcus.

An experiment was conducted using rapid

readers to investigate the reading of sentences. When a subject read at an extremely rapid rate, neural activity in the language areas of the left hemisphere decreased, suggesting the subject's strategy of reading rapidly while omitting phonological processes. In addition, we introduced new experiments to examine the interaction between the processing of two words using priming paradigms, as an initial step in modeling the various language processes. Since language processes are accomplished by a complex network involving multiple processing elements, we would like to investigate the algorithm of this network through quantitative modeling. The clarification of a quantitative model of the brain is expected to contribute to improvements in the human interfaces of information and communications as well as in the design of easy-to-use information-processing systems. Moreover, contributions to medical applications may also be possible through a comparison of the models with diagrams obtained from

lesion studies. If a model could be constructed to simulate the behavior of the brain with sufficient accuracy, it is believed that this model could lead to artificial language functions on a level comparable to that seen in humans. If we could also incorporate elements of intention, value judgments, and so on into the model, realization of true artificial intelligence (i.e., a machine that responds virtually indistinguishably from a human subject) may become possible, albeit in the far future.

Acknowledgements

We are thankful to Prof. Yoichi. Okabe of the University of Tokyo, for providing the SMN and for his participation in discussions; Assistant Prof. Ayumu Matani of the same university, who carried out collaborative research in priming experiments, and Dr. Toyofumi Sasaki, President of Japan Society of Speed Reading Education, who carried out collaborative research in rapid reading.

References

- 1 N. Fujimaki et al., "Functional magnetic resonance imaging of neural activity related to orthographic, phonological, and lexico-semantic judgments of visually presented characters and words", *Human Brain Mapping*, Vol. 8, pp. 44-59, 1999.
- 2 N. Fujimaki et al., "MEGs during judgment of visual characters --- Comparison with fMRI ---", *Proceedings of the 11th International Conference on Biomagnetism*, pp. 664-667, 1999.
- 3 S. Munetsuna et al., "Comparison of the activation area measured by MEG and fMRI in human primary somatosensory cortex (In Japanese)", *The Journal of Japan Biomagnetism and Bioelectromagnetics Society*, Vol. 16, pp. 226-227, 2003.
- 4 N. Fujimaki et al., "An fMRI-constrained MEG source analysis with procedures for dividing and grouping activation", *NeuroImage*, Vol. 17, pp.324-343, 2002.
- 5 C-H. Im et al., "fMRI constrained MEG source imaging and consideration of fMRI invisible sources", presented at *Biomag 2004*, Aug. 9-12, 2004, Boston.
- 6 N. Fujimaki et al., "Lexical judgments analyzed using fMRI-constrained MEG-dipoles", presented at *KIT International Symposium on Brain and Language*, Dec. 12-13, 2002, Kanazawa, Japan.
- 7 N. Fujimaki et al., "Right-lateralized neural activity during inner speech repeated by cues", *NeuroReport*, Vol. 15, pp. 2341-2345, 2004.
- 8 T. Hayakawa et al., "Information flow related to visual search assessed using magnetoencephalography", *Cogn. Brain Res.*, 15, pp. 285-295, 2003.
- 9 T. Hayakawa et al. "Activity of the human visual cortex during visual search task assessed by an MEG multipole analysis with fMRI position constraints (In Japanese)", *Proceedings of The 17th Symposium on Biological and Physiological Engineering*, pp. 182-185, 2002.
- 10 N. Fujimaki et al., "Neural activation dependent on reading speed during covert reading of novels", *NeuroReport*, Vol. 15, pp. 239-243, 2004.
- 11 T. Hayakawa et al., "Semantic contextual effects on early neural activities for visual-word processing", presented at *Biomag 2004*, Aug. 9-12, 2004, Boston.
- 12 N. Fujimaki et al., "Magnetic responses to visually presented words with masked repetition priming", presented at *Biomag 2004*, Aug. 9-12, 2004, Boston.
- 13 A. Matani et al., "MEG latency difference measurement for priming experiments", presented at *Biomag 2004*, Aug. 9-12, 2004, Boston.
- 14 Y. Naruse et al., "Analysis of phase-sorted single trials at peak alpha frequency", presented at *Biomag 2004*, Aug. 9-12, 2004, Boston.



FUJIMAKI Norio, Ph.D.

*Senior Researcher, Brain Information
Group, Kansai Advanced Research
Center, Basic and Advanced Research
Department
Neural Science*



HAYAKAWA Tomoe, Ph.D.

*Expert Researcher, Brain Information
Group, Kansai Advanced Research
Center, Basic and Advanced Research
Department
Neural Science*