Linking semantic priming effect in functional MRI and event-related potentials

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The aim of this study is to examine the neural substrates involved in semantic priming using a combined event-related functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) study. Twelve subjects were instructed to judge whether the presented target word was a real word or a nonword. Under the related condition, target words were preceded by a semantically related prime word. On the other hand, under the unrelated condition, prime words did not have semantic relatedness with the target word. The reaction time for reaching a judgment was longer under the unrelated condition than under the related condition, indicating that the recognition of target words is promoted by semantic priming under the related condition. In the fMRI results, we found reduced activity in the dorsal and ventral left inferior frontal gyrus, the anterior cingulate, and left superior temporal cortex for related versus unrelated conditions (i.e., the repetition suppression effect). ERP analysis revealed that the amplitude of the N400 component was reduced under the related condition compared with the unrelated condition (i.e., the N400 priming effect). Correlation analysis between the BOLD repetition suppression effect and the N400 priming effect decomposed by independent component analysis (ICA) across subjects showed significant correlation in the left superior temporal gyrus. This finding is consistent with the recent MEG data suggesting that the source of N400 is judged to be the bilateral superior temporal lobe. We discussed this finding herein in relation to the modulation of access to the phonological representation caused by semantic priming.
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Introduction

Semantic priming is a phenomenon in which a target word (e.g., "nurse") is recognized more rapidly when it is preceded by a semantically related word (e.g., "doctor") than when it is preceded by an unrelated word (e.g., "bread"). A number of psychological studies have investigated the cognitive basis of this phenomenon and demonstrated that semantic priming consists of several cognitive processes. Neely (1991) suggested that semantic priming results from automatic and controlled processing mechanisms. In the former, known as "automatic spreading activation", the presentation of prime words can activate the corresponding semantic representations with subsequent spread to and automatic activation of related nodes, thereby facilitating recognition when a semantically related word is presented. In the latter, controlled semantic processing involving prelexically developed expectancies and postlexical semantic matching is under conscious control. Subjects develop expectancies regarding the recognition of the prime word, leading to attention directed to semantically related words. Therefore, subsequent processing of a related word is promoted, whereas processing of an unrelated (unexpected) word is inhibited. Another study by Neely (1977) suggests that automatic spreading activation is invoked when the interval between presentation of prime and target words (i.e., stimulus onset asynchrony; SOA) is short, while controlled processes are engaged when the SOA is greater than 400 ms.

In recent years, several studies employing single cell recordings and functional imaging techniques, such as fMRI and PET, have been used to investigate the neural basis of priming and have revealed that repetition priming inhibits activity in those brain regions that process a presented stimulus (Badgaiyan et al., 1999; Buckner et al., 2000; Desimone, 1996; Thiel et al., 2001). For example, Desimone (1996) showed that repeated stimuli resulted in decreases in neural firing in the infero-temporal neurons of macaque monkeys and referred to this phenomenon as "repetition suppression" (Henson, 2003). Desimone (1996) also proposed that

a repeated stimulus produces a "sharpening" of its cortical representation, whereby neurons that code features that are unnecessary for processing the stimulus become progressively less responsive. This results in a reduction in the firing rate of a population of neurons and a decrease in the neuronal activity from that region of the cortex.

Recent studies of semantic priming in event-related fMRI showed clear repetition suppression in the left inferior frontal gyrus and in the middle or superior temporal gyrus. Event-related design reduces the effect of modes that are not sensitive to semantic relations between word pairs per se (e.g. strategies or attention) from the semantic priming effect. For instance, Kotz et al. (2002) conducted an event-related fMRI experiment to investigate the neural basis of auditory semantic priming and reported that the activation of the left inferior frontal gyrus was lower in the related condition than in the unrelated condition. Copland et al. (2003) also characterized the repetition suppression effect in the left inferior frontal cortex during a visual semantic priming task. The left inferior frontal gyrus participates in the semantic processing of words or objects, and a number of repetition priming studies have shown that the activity of this region is attenuated by priming (Buckner et al., 1995, 2000; Donaldson et al., 2001; Thiel et al., 2001; Wagner et al., 2000). Kotz et al. (2002) suggested that the repetition suppression effect in the left inferior frontal gyrus is due to reduced demand for semantic memory retrieval or the result of selection caused by the automatic and/or controlled semantic priming effect. Furthermore, significant repetition suppression has been observed in the left anterior medial temporal cortex (Rossell et al., 2003) and superior temporal gyrus (Rissman et al., 2003) during a semantic priming task, suggesting that the left medial and superior temporal gyrus is associated with the preservation of the word's representation and that the repetition suppression in these regions is due to the preceding activation of target word representation caused by automatic spreading activation.

Semantic priming has also been investigated using neurophysiological methods, such as event-related potentials (ERPs). ERP studies have shown that semantic priming affects the amplitude of an ERP component called N400, which is a negative deflection of the ERP signal between 300 and 500 ms, peaking at about 400 ms after stimulus presentation (Kutas and Hillyard, 1980). N400 is sensitive to semantic deviation, with larger N400 amplitudes corresponding to semantically incongruent words at the sentence and word level processing (Kutas and Hillyard, 1980). In the semantic or repetition priming paradigm, N400 is reduced when target words are preceded by semantically related primes or by the same word (N400 priming effect) (Holcomb, 1993; Kiefer and Spitzer, 2000; Van Petten, 1993).

There are two main hypotheses concerning the cognitive basis of N400. The lexical hypothesis states that N400 reflects the activation of the lexical and/or semantic representation of a word (Fischler and Raney, 1989; Van Petten and Kutas, 1987), while the postlexical hypothesis suggests that N400 reflects an associative process that integrates word representation with ongoing context (Holcomb, 1993; Neville et al., 1991; Rugg and Doyle, 1994). Thus, the N400 priming effect may result from the ease of integrating information into a context or from the access to word representation caused by controlled or automatic semantic priming.

Several studies have suggested that N400 is generated from a number of different regions (Guillem et al., 1999; Nobre and McCarthy, 1995; Nobre et al., 1994). Intra-cranial depth recording of ERP emphasized the importance of the medial temporal cortex, including the amygdala and hippocampus, in the generation of N400 (Guillem et al., 1999; McCarthy et al., 1995). McCarthy et al. (1995) suggested that N400 is generated from the neocortex near the collateral sulcus, including the anterior fusiform and parahippocampal gyri. However, intra-cranial recordings from other structures have shown that cortical areas along the superior temporal sulcus are involved in the generation of N400 (Halgren et al., 1994). Furthermore, a number of magnetoencephalography (MEG) studies have suggested that N400 originates in the bilateral superior temporal gyrus in the vicinity of the auditory cortex, with the signal being stronger in the left hemisphere than in the right hemisphere (Helenius et al., 1998, 2002; Laine et al., 2000; Sekiguchi et al., 2001; Simos et al., 1997). Helenius et al. (1998) found that semantic deviation in sentence reading elicited magnetic fields at 350–450 ms after word onset (N400m) and suggested that this process was mediated by the bilateral superior temporal gyrus. Sekiguchi et al. (2001) reported that repetitive presentation of visual words reduced the magnetic field associated with the left superior temporal gyrus adjacent to the auditory cortex, suggesting that the superior temporal gyrus mediates generation and priming effect on N400m. Furthermore, Marinkovic et al. (2003) used a distributed source modeling technique to demonstrate that the priming effect on N400m is mediated via the left superior temporal gyrus and the left inferior frontal gyrus. These results are consistent with observations from fMRI studies, which reported that the semantic priming caused a repetition suppression effect in the left inferior frontal cortex and the left middle or superior temporal cortex. However, the relationship between the repetition suppression effect in the BOLD signal and the N400 priming effect remains unclear.

Rossell et al. (2003) studied the neural distribution of semantic priming using a combination of fMRI and ERP and a short and long interval between prime and target items in order to manipulate the degree of semantic expectancies. They showed a significant repetition suppression in the anterior medial temporal lobe with the N400 priming effect associated with the centro-parietal regions, indicating the relationship between the activity of the anterior medial temporal cortex and N400 generation. Furthermore, the effect of the prime-target SOA difference was reflected in the anterior cingulate cortex in their study. However, they recorded ERP and fMRI data from different groups of subjects, making it impossible to directly characterize the relationship between the effect of semantic priming in BOLD activity and the ERP component.

In the present study, we employed ERP and event-related fMRI recording in separate sessions and in the same subjects in order to investigate the correlation between the magnitude of the N400 priming effect and the repetition suppression effect in the BOLD signal caused by semantic priming. Since recent fMRI study has suggested that similar BOLD responses were evoked when repeating the same experiment (Wei et al., 2004), it is reasonable that ERP and fMRI data measured in separated sessions are integrated in our analysis. The correlation analysis between the BOLD signal and an ERP component provide an alternative method of examining the relationship between the neural activity in a specific brain region and an ERP component (Horovitz et al., 2002; Liebenthal et al., 2003; Opitz et al., 2001). Further, this correlation analysis may identify the N400 priming effect in a different manner than the equivalent current dipole (ECD) and distributed source modeling methods used in MEG and EEG studies. We conducted the correlation analysis in seven regions.

Four of these regions have been associated with N400 generation in previous studies, and the other regions showed significant repetition suppression effects in whole brain subtraction analysis. Furthermore, we used a new ERP analysis technique, independent component analysis (ICA), to eliminate the contamination of N400 by other ERP components. ICA enables us to conduct blind source separation of a linear mixture of sources in an electroencephalogram that is spatially fixed and temporally independent. Components were determined using a neural network in order to train unmixed weighted matrices that maximize the joint entropy between nonlinearly transformed channel data (Makeig et al., 1997). By using ICA, other components that overlap N400 based on the scalp distribution were excluded, thereby resulting in a more precise examination and correlation analysis.

Based on previous studies (Horovitz et al., 2002; Liebenthal et al., 2003; Opitz et al., 2001) that demonstrated that ERP amplitude correlated with BOLD activity across subject, we hypothesized that the repetition suppression effect would be reflected in BOLD activity. Further, the subjects with greater BOLD repetition suppression effect in regions related to N400 generation would show greater N400 priming effect, and the regions involved in the semantic priming, such as the inferior frontal gyrus and the superior or middle temporal gyrus of the left hemisphere, would show significant repetition suppression effects in BOLD response, the magnitude of which would correlate with the N400 priming effect.

Materials and methods

Subjects

Electrophysiological and hemodynamic brain responses were measured in 12 healthy right-handed volunteers (six males and six females, mean age ± SD, 20.8 ± 1.6 years). Half of the subject group participated in the fMRI experiment before the ERP recording, and the other half of the subject group took part in the fMRI experiment after the ERP experiment. Data from subject was excluded from fMRI analysis because of an excess of head motion artifacts. Before the experiment, written informed consent was obtained from all subjects. This study was approved by the ethics committee of the National Institute for Physiological Sciences.

Materials

Stimuli consisted of 400 Japanese three-letter nouns and 70 pronounceable pseudo-words. All stimuli were presented visually in Katakana script (a Japanese syllabic script) that were arranged into 230 prime-target pairs; 80 pairs contained semantically related words, another 80 pairs contained semantically unrelated words, and the remaining 70 pairs had words followed by pseudo-words. The stimuli were divided into two shorter lists (Lists 1 and 2), with each list containing 40 semantically related pairs (related), 40 semantically unrelated pairs (unrelated), and 35 word–pseudo-word pairs (pseudo). Assignment of the list to ERP and fMRI recording was counterbalanced across subjects. Word frequency (Amano and Kondo, 2000) was controlled for target words across each condition and list. After the experiment, the strength of the semantic relationship of each pair was evaluated in all subjects using a 5-point scale. Table 1 summarizes the information regarding stimulus material. Two-way ANOVA (List × Condition) revealed a significant main effect of Condition ($F(1,9) = 311.86$,

Table 1
Mean and standard deviation of word familiarity of target words and strength of prime-target semantic relatedness

List	1		2	
Condition	Related	Unrelated	Related	Unrelated
Word familiarity	5.94 (0.45)	5.79 (0.45)	5.92 (0.38)	5.84 (0.37)
Strength of semantic relatedness	3.94 (0.52)	1.22 (0.30)	4.00 (0.31)	1.18 (0.19)

$P < 0.0000001$), suggesting that the strength of the semantic relationship in related word pairs was significantly larger than that in unrelated word pairs. No main effect of the List was observed.

Experimental procedure

During the task, 40 related, 40 unrelated, and 35 pseudo-events were randomly presented along with 35 null events and fixation points in two separate runs. After the presentation of fixation for 400 ms, a prime word was presented for 400 ms followed by an inter-stimulus interval of 200 ms and a target word that was presented for 1000 ms. The inter-trial interval was 3000 ms. Trial scheme is illustrated in Fig. 1. Subjects were instructed to decide whether the target word was a real word or a pseudo-word by pressing unique buttons, and subject responses and reaction times were recorded. An identical task procedure was used in for both the ERP and the fMRI experiments.

The behavioral semantic priming effect was assessed by repeated measures analysis of variance (ANOVAs), with comparison of the condition (related, unrelated) and recording (ERP, fMRI) with reaction time. Post hoc comparisons were conducted using the Least Significant Difference (LSD) test.
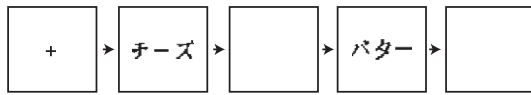
ERP experiment

The electroencephalograph was recorded from 14 international 10–20 system scalp locations (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, T5, T6, Oz, O1, O2) that were referenced to the tip of the nose. Eye movement was monitored by an electrode placed on the supra-ridge of the left eye. Inter-electrode impedances were set below 5.
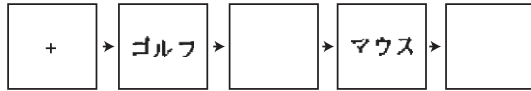
The EEG and EOG data were filtered using a bandpass of 0.5–60 Hz. The data were digitized with an A–D conversion rate of 1000 Hz and sampled from a 300-ms preceding target word in a trial until 1400 ms after the stimulus onset. Digital codes were sent from the stimulus-presentation computer to mark the onset and type of each target stimulus. EEG data were corrected to a 100-ms baseline prior to the onset of the target word. Trials in which the EEG or eye movements exceeded plus or minus 50 μV were automatically rejected from the averaging process. ERPs were analyzed using repeated measures ANOVAs that were conducted on the mean amplitude of a 300–500 ms time window to compare factors of condition (related, unrelated) and the electrode (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, T5, T6, Oz, O1, O2). In the present study, semantic priming seems to affect the latency of the late positive component (LPC) as well as the amplitude of N400. Therefore, we assessed the peak latencies and amplitudes of LPC at Fz, Cz, and Pz. According to their appearance in the grand average waveforms, the LPC peak was defined as the most positive voltage within the interval of 450–700 ms. The analysis was performed to compare factors of condition (related, unrelated) and the electrode
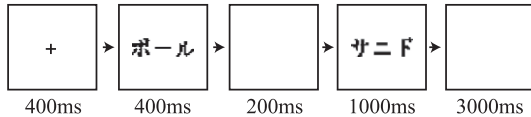
(1) Stimulus Presentation

(a) Related Condition

| + | → | チーズ | → | | → | バター | → | |

(b) Unrelated Condition

| + | → | ゴルフ | → | | → | マウス | → | |

(c) Nonword Condition

| + | → | ボール | → | | → | サニド | → | |

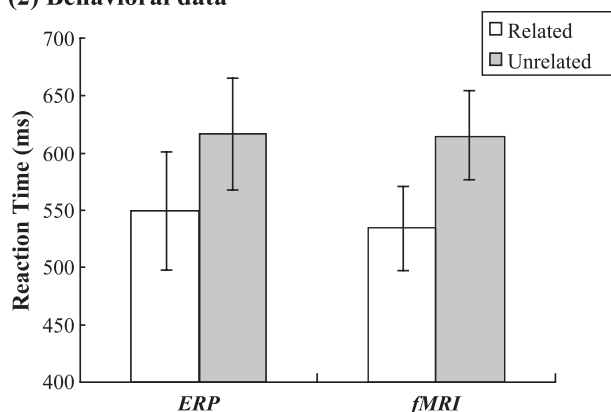400ms   400ms   200ms   1000ms   3000ms

(2) Behavioral data

Fig. 1. (1) Task scheme: subjects were asked to judge whether or not the target word is a real word. Under the related condition (the prime word means "cheese"; the target word means "butter"), the prime word and the target word semantically related, while with the unrelated condition (the prime word means "golf"; the target word means "mouse"), there was no semantic relation between the prime word and the target word. Under the nonword condition, a nonword was presented as a target word (prime word means "ball"). (2) Behavioral results: mean RT and standard errors for the related and unrelated target words in the ERP and fMRI sessions.

(Fz, Cz, Pz). The Geisser–Greenhouse correction was always applied when evaluating effects with more than one degree of freedom were present in the numerator. Post hoc comparisons were conducted using the Least Significant Difference (LSD) test.

Correlation analysis was conducted using a component decomposed by ICA to diminish the effect of other component, such as LPC. The difference wave of an unrelated minus-related condition was computed for each subject in order to monitor the N400 priming effect elicited by semantic priming. After the decomposing original waveforms of 12 subjects were characterized, the amplitude of the N400 priming effect was correlated with signal changes measured by fMRI. The LPC of the related condition peaked earlier than that of unrelated condition; therefore, the later part of the N400 priming effect on difference waves could be contaminated by the effect of the LPC latency difference. In order to diminish the effect of the LPC and/or other components from the difference wave, we applied ICA to difference wave data. The ICA was conducted using Psychophysiological Analysis Software ver. 4.0, provided by the Computational Neuroscience

Laboratory of the Salk Institute, CA, USA, (http://www.cnl.salk.edu/~tewon/ica_cnl.html) implemented in MATLAB version 6.1 (Mathworks). We conducted a single ICA analysis with concatenated data from all subjects. This analysis enabled us to obtain the N400 priming effect that has the same scalp distribution for all subjects. After the ICA decomposition, a component that was dominant at the centro-parietal region (IC1) was chosen from 14 decomposed components, and the peak amplitude within 350–450 ms in the component was assessed in all subjects and used for correlation analysis. Finally, correlation analysis was performed on the differences of standard N400 amplitude (e.g., the mean amplitude of 300–500 ms time window) to investigate whether a correlation was present only when ICA was applied to the data.

fMRI experiment

fMRI data acquisition and analysis

Functional images of the whole brain were acquired in an axial orientation using a 3-T Siemens Allegra MRI scanner equipped with a single-shot EPI (TR = 2.3 s, TE = 30 ms, Flip Angle = 80°, 64 × 64 matrix and 26 slices, voxel size = 3 × 3 × 4 mm) sensitive to BOLD contrast (Ogawa et al., 1992). After discarding the first six images, the next 166 successive images in each run were subjected to analysis. An anatomical T1-weighted image was also acquired (MPRAGE, TR = 3 s, TE = 4.6 ms, Flip Angle = 90°, 256 × 256 matrix and 26 slices, voxel size = 0.75 × 0.75 × 4 mm) for each subject. The fMRI experiment was controlled using Presentation software (Neurobehavioral Systems Inc. Albany, CA, USA).

Data were analyzed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK). First, all volumes were realigned spatially to the last volume, and the signal in each slice was realigned temporally to that obtained in the middle slice using a sinc interpolation. The resliced volumes were normalized to the standard space of Talairach and Tournoux (1988) using a transformation matrix obtained from the normalization process of the T1-weighted anatomical image of each individual subject to the T1 template image. The T1-weighted anatomical image was coregistered to the mean EPI image in each subject. The normalized images were spatially smoothed using an 8-mm Gaussian kernel. Following pre-processing, statistical analysis of each individual subject was conducted using the general linear model. The hemodynamic response triggered by the target word in each condition was modeled with two-basis function, that is, a hemodynamic response function (HRF) and its temporal derivative. Low-pass and high-pass frequency filters were applied to the time-series data. The images were scaled to a grand mean of 100 over all voxels and scans within a session. In the subtraction analysis, four conditions (correct response for related target, correct response for unrelated target, correct response for pseudoword response, and incorrect response) were modeled separately. Parameter estimates for each condition and for the difference between the conditions were calculated from the least-mean-square fit of the model to the time-series data. Images of parameter estimates representing event-related activity at each voxel for each condition and each subject were created.

At the second level, the results for each subject were entered into the random effects model by applying t tests between the contrast images to create a group statistical parametric map (SPM). An SPM of voxels showing a significant response to stimulus presentation versus the baseline and differences in the response between the conditions was also created.

Table 2
Brain areas demonstrating significant repetition suppression in whole brain analysis

Region name (BA)	L/R	x, y, z	t value
Dorsal inferior frontal gyrus (45)	L	−50, 28, 14	7.75
Ventral inferior frontal gyrus (47)	L	−30, 22, −10	7.22
Anterior cingulate cortex (8/32)		0, 26, 44	6.81

Whole brain analysis

The first analysis was performed by entering contrast images containing parameter estimates of the difference in activity between the related and unrelated conditions into a one-sample t test to reveal the hemodynamic repetition suppression, that is, the unrelated condition versus the related condition. Since we had assumed that several brain regions (e.g. left inferior frontal cortex) would show significant repetition suppression effect, the statistical threshold was set at $P = 0.001$ without corrections for multiple comparisons. The extent threshold was set at $k = 10$ voxels. Region names, coordinates, and Z values are summarized in Table 2. The distributions of regions that showed significant hemodynamic repetition suppression are illustrated in Fig. 4.

ROI analysis

Three regions that showed significant repetition suppression in whole brain analysis were selected as regions of interest (ROIs) [the dorsal left inferior frontal gyrus (−50, 28, 14), the ventral left inferior frontal gyrus (−30, 22, −10), and the anterior cingulate cortex (0, 26, 44)]. For each location, a three-dimensional-ROI was defined to include all voxels within a sphere of 8 mm radius by using MarsBar software (http://www.mrc.cbu.cam.ac.uk/Imaging/marsbar.html).

In addition, eight regions that were thought to be associated with the generation of N400 in previous studies were selected as ROIs. These regions included the amygdala–hippocampus (−23, 0, −18), the anterior fusiform gyrus (−30, −21, −21), anterior medial temporal cortex (−40, 14, −34) and the superior temporal gyrus (−57, −12, −1) of the left hemisphere and the correspond-

ing regions of the right hemisphere. In these regions, magnitude of activation was extracted from an 8-mm spherical ROI centered on each coordinate. These coordinates were derived from McCarthy et al. (1995), Rissman et al. (2003), and Rossell et al. (2003).

First, for eight regions, *t* tests between conditions were performed on the signals obtained in each ROI to investigate the repetition suppression effect that was not characterized by whole brain subtraction analysis. Second, we addressed the question of whether the magnitude of the N400 priming effect measured by ERP would correlate with repetition suppression of the BOLD signal in these ROIs. The contrast images of 11 subjects pertaining to the difference in activity between the unrelated and related conditions and the amplitude of independent components derived from the unrelated–related difference wave in each subject were entered into a simple regression analysis.

Results

Behavioral data

Behavioral data from ERP and fMRI sessions are presented in Fig. 1. There was a significant main effect on reaction time of condition ($F(1, 11) = 64.85$, $P < 0.00001$). Post hoc analysis revealed significant semantic priming, as measured by diminished reaction time for related conditions compared with unrelated conditions under both ERP and fMRI experiments ($P < 0.000001$). Neither the main effect due to recording nor priming × recording interaction was significant.

ERP data

Grand-averaged waveforms elicited by targets under the related and unrelated condition from all electrodes are shown in Fig. 2. The amplitude of N400 was reduced under the related condition as compared to the unrelated condition. ANOVA of the mean amplitude of the 300–500 ms time window revealed a significant main effect of condition ($F(1, 10) = 23.10$, $P < 0.001$), a main effect of the electrode ($F(2.6, 21.2) = 16.64$, $P < 0.000001$), and condition ×
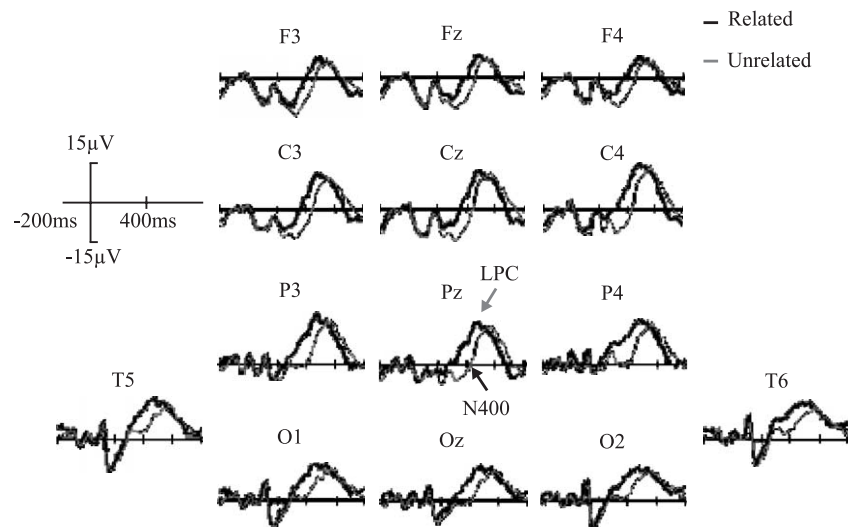

Fig. 2. Grand-averaged ERP under the related and unrelated condition at all sites. Positive polarity is plotted upward. Waveforms elicited by the target words are depicted. The N400 component (black arrow) is attenuated under the related condition, and the LPC peak (gray arrow) is delayed under the unrelated condition.

(1)

Unrelated–Related
Difference wave

Fz

Cz

Pz

(2)

Decomposed component

10 μV

400ms   800ms

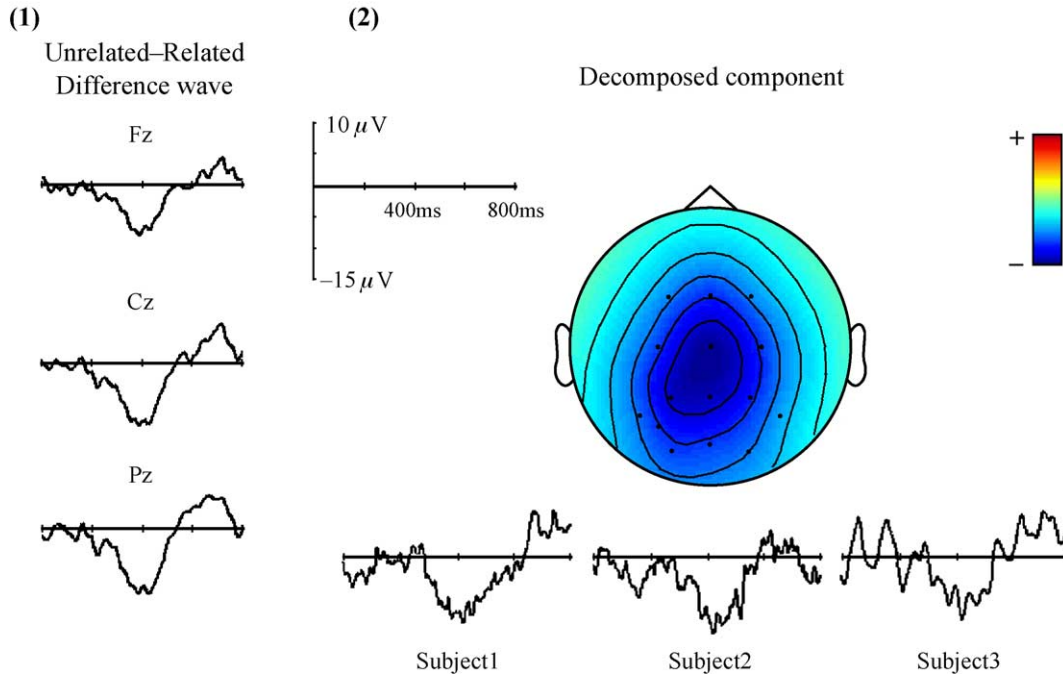−15 μV

Subject1   Subject2   Subject3

Fig. 3. (1) Difference waves between the unrelated and related conditions at the Fz, Cz, and Pz sites. Negative component peaking between 350 and 450 ms is observed at all sites. Decomposed component and the scalp distribution. The component obtained from a single ICA with concatenated data from all subjects and the time course of the activity from three representative subjects are shown. The component is dominant at the centro-parietal region and peaked between 350 and 450 ms.

electrode interaction ($F(13, 130) = 3.21$, $P < 0.0001$). Post hoc analysis revealed that N400 was significantly larger for the unrelated condition than for the related condition at all sites ($P < 0.000001$). Unrelated–related difference waves are depicted in Fig. 3 (left panel). The peak latency of LPC was slightly delayed under the unrelated condition, but the difference did not reach statistical significance ($F(1, 11) = 4.72$, $P < 0.1$). There was no significant effect in LPC peak amplitude. Fig. 3 shows the ICA component derived from concatenated data from all subjects and the scalp distribution.

Imaging data

Whole brain analysis

We hypothesized that regions showing greater activation under the unrelated condition than under the related condition were involved in repetition suppression induced by semantic priming. As shown in the top panel of Fig. 4, when contrasted with the unrelated condition, the related condition was associated with decreased activity in the anterior cingulate cortex (BA 8/32), the

Unrelated - Related Condition

(A) Dorsal LIFG
[-50, 28, 14]

0.4
0.3
0.2
0.1
0

related   unrelated

(B) Ventral LIFG
[-30, 22, -10]

0.4
0.3
0.2
0.1
0

related   unrelated

(C) ACC
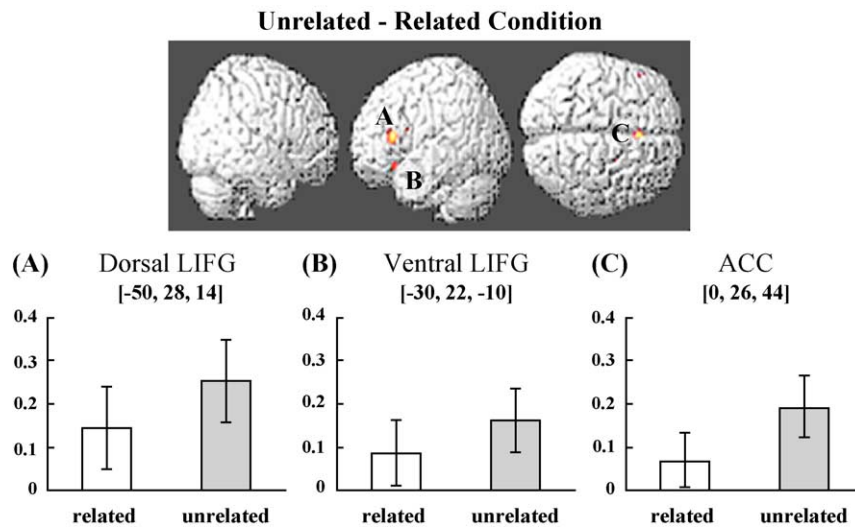[0, 26, 44]

0.4
0.3
0.2
0.1
0

related   unrelated

Fig. 4. Brain areas demonstrating significant repetition suppression in whole brain analysis. Activations are displayed on a surface rendering of a typical brain (top panel). The dorsal part of the left inferior frontal gyrus (A), the ventral part of the left inferior frontal gyrus (B), and the anterior cingulate cortex (C) are more strongly activated under the unrelated condition than under the related condition. Lower graphs depict the mean percent signal change (column) and the standard deviation (bar) in the peaks of these regions.

dorsal left inferior frontal cortex (BA 45), and the ventral left inferior frontal cortex (BA47). In contrast, no region exhibited greater activation under the related than under the unrelated condition at this threshold.

ROI analysis

The activation patterns in four priori ROIs and the regions that showed significant repetition suppression effect were examined. These included regions within the amygdala, the anterior fusiform gyrus, the superior temporal gyrus, the anterior medial temporal lobe, the dorsal left inferior frontal gyrus, the ventral left inferior frontal gyrus, and the anterior cingulate cortex. t tests were conducted separately for the priori ROIs with regard to activation. For the left superior temporal gyrus, activation for the unrelated condition was significantly larger when compared with that for the related condition (t (10) = 2.49, $P < 0.05$), while the difference was not significant in the right hemisphere (t (10) = 1.26, $P > 0.2$). The result indicates that the repetition suppression is predominant in the left hemisphere. There was no significant repetition suppression effect in the amygdala–hippocampus, anterior fusiform gyrus, or anterior medial temporal lobe, in either hemisphere.

The superior temporal gyrus in the left hemisphere exhibited significant positive correlation between the magnitude of the N400 priming effect and the BOLD repetition suppression effect. Subjects that showed a greater N400 priming effect exhibited a greater BOLD repetition suppression effect in the left superior temporal gyrus ($r = 0.72$, $df = 9$, $P < 0.05$). Although the dorsal and ventral inferior frontal gyrus and the anterior cingulate gyrus showed a significant BOLD repetition suppression effect, the magnitude of BOLD response did not correlate with the amplitude of N400 priming effect across subjects (see Fig. 5). There was no significant BOLD-N400 correlation in the anterior fusiform gyrus, anterior medial temporal lobe and amygdala. Furthermore, N400 priming effect assessed by standard N400 amplitude measures did not show significant correlation with the repetition suppression effect in all ROIs.

Discussion

The goal of this study was to characterize the neural basis of the N400 priming effect in semantic priming. We recorded ERP and fMRI from the same group of subjects in separate sessions and conducted correlation analysis between the N400 priming effect decomposed by ICA and the BOLD repetition suppression effect. In the whole brain analysis, we found that semantic priming caused repetition suppression in the dorsal and ventral part of the left inferior frontal gyrus and in the anterior cingulate cortex. Further, ROI analysis showed significant repetition suppression in the left superior temporal gyrus. Correlation analysis revealed that the magnitude of the N400 priming effect was correlated with the activity in the left superior temporal gyrus.

The behavioral results showed a clear semantic priming effect during the lexical decision task. That is, the reaction time for the target word preceded by a semantically related word was shorter than that for the target word preceded by a semantically unrelated word, suggesting that semantic priming facilitated the processing of the target word.

The present study demonstrated that the amplitude of N400 was attenuated by semantic, which is consistent with observations by other investigators (Anderson and Holcomb, 1995; Bentin, 1987; Bentin et al., 1985; Hill et al., 2002; Holcomb and Anderson,

1993). The ERP waveforms of the present study and the scalp distribution resemble that reported by Rossell et al. (2003). Although the amplitude of N400 was attenuated by semantic priming, the present study also demonstrated that semantic priming effect resulted in delayed peak latency of the late positive component (LPC) under the unrelated condition. According to Bentin et al. (1985), mechanisms that evoke the LPC component in lexical decisions can be interpreted as P300, which is associated with response decisions or the updating of working memory (Kok, 2001). Thus, it seems plausible that LPC latency is delayed under the unrelated condition because a lexical decision requires a more demanding process for decisions or for the evaluation of a target word under the unrelated condition than under the related condition. However, the delay of the LPC peak caused by semantic priming could contaminate the N400 priming effect in the unrelated–related difference wave and make it difficult to identify the source of N400. Therefore, we used ICA to exclude components that have inappropriate temporal or spatial distribution in the difference wave for each subject, thereby avoiding contamination of the other ERP components by the obtained N400 priming effect and resulting in a more precise correlation analysis for identification of the neural basis of the N400 priming effect. The N400 priming effect assessed by the original N400 waveform did not have significant correlation with the repetition suppression effect in all ROIs, suggesting that the original waveforms might be contaminated with other components.

Whole brain fMRI analysis showed that there was significant hemodynamic repetition suppression effect in the dorsal and ventral left inferior frontal gyrus and in the anterior cingulate cortex. The anterior medial temporal activity, which displayed significant repetition suppression effect in Rossell et al. (2003), did not differ between the related and unrelated condition. Whereas Rossell's study used a fixed-effects analysis, the present study used a random-effects analysis. Friston et al. (1999) indicated that fixed-effect analysis can yield results different from those obtained from random-effects analysis, because the fixed-effects analysis is more sensitive than the random-effects analysis. Thus, it is possible that the difference of analysis technique (i.e. fixed-effects model vs. random-effects model) contributed to the difference in results between the present study and those reported by Rossell et al.

The left inferior frontal gyrus has been of particular interest to researchers because of its strong association with the semantic processing of words or objects. However, it is unlikely that this region mediates the preservation of semantic memory representation, since lesions in this region do not cause deficits in semantic knowledge (Gershberg, 1997; Swick, 1998). The left inferior frontal gyrus mediates selection among competing alternatives regulated by semantic knowledge, recent experience (Thompson-Schill et al., 1997) or the central executive of retrieval of semantic representation from semantic memory (Wagner et al., 2001). Thus, the semantic priming effect (i.e., the repetition suppression effect) of the left inferior frontal gyrus indicates that the selection or retrieval of semantic representation for unrelated targets is more demanding than that for related targets, possibly because the processing of target words preceded by a semantically related word was facilitated by conscious and unconscious priming effects, such as automatic spreading activation or the expectancy effect.

Some researches have reported that the dorsal and ventral parts of the left inferior frontal gyrus play different roles in semantic processing (Bokde et al., 2001; Noppeney and Price, 2002). Noppeney and Price (2002) suggested that the ventral part of left
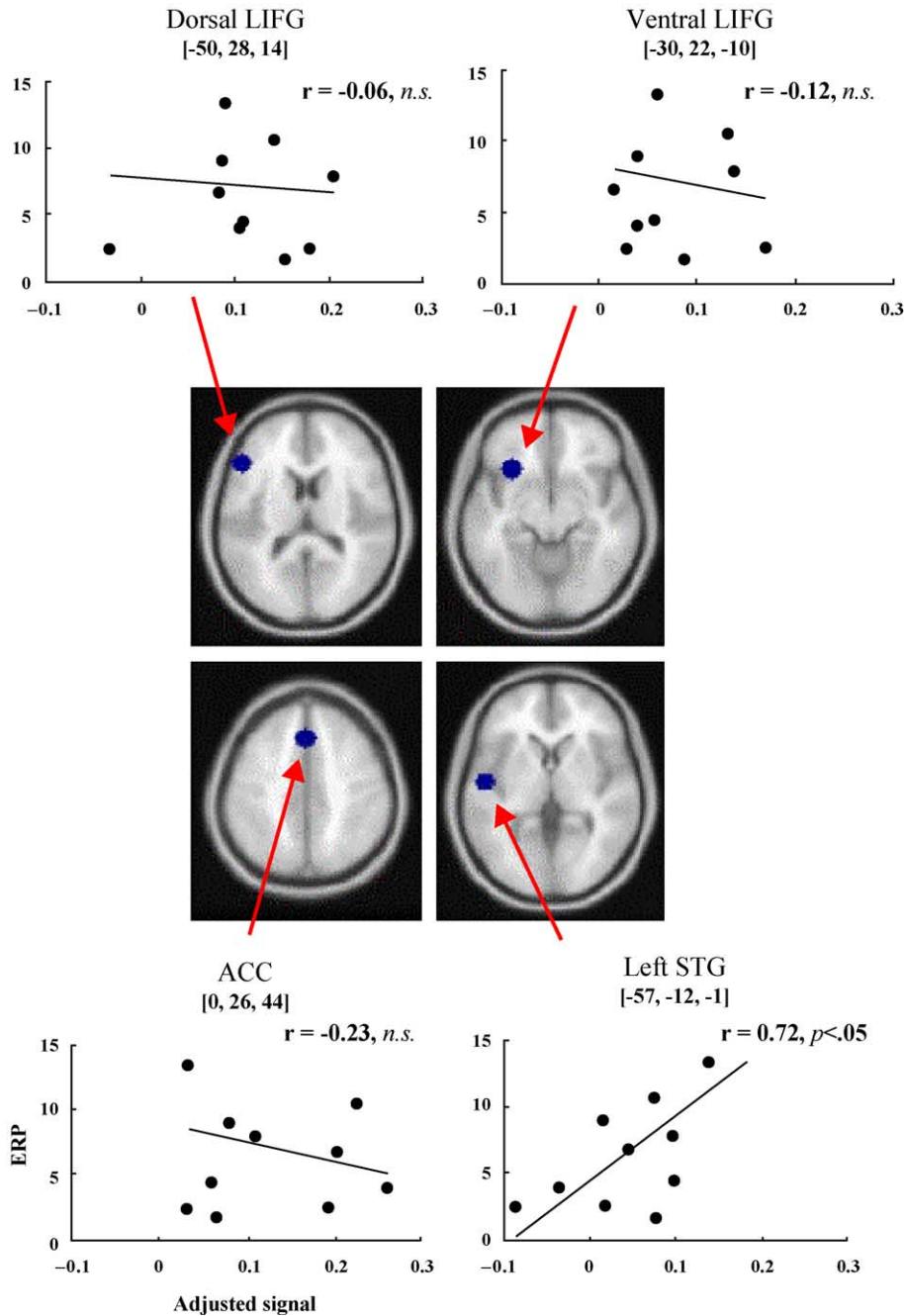
Fig. 5. Correlation between the magnitude of repetition suppression on BOLD and the magnitude of the N400 priming effect in the regions that show significant repetition suppression. The horizontal axis represents the magnitude of the repetition suppression effect, and the vertical axis represents the magnitude of the N400 priming effect. The correlation is significant only at the left superior temporal gyrus.

anterior inferior frontal gyrus is involved in semantic retrieval or in the semantic evaluation of stimulus, while the dorsal left inferior frontal gyrus is associated with the general processing of semantic or phonological information. Although we found significant repetition suppression effect in the ventral part of the left inferior frontal gyrus (BA47) and in the dorsal part of the left inferior frontal gyrus (BA45), other visual semantic priming studies have not found the repetition suppression effect in the dorsal part of the inferior frontal gyrus (Copland et al., 2003; Rossell et al., 2003). For example, Copland et al. (2003) found significant repetition suppression effect only in the ventral left inferior frontal gyrus

(BA47). We speculate that the discrepancy between the results of present study and those of Copland et al. (2003) can be attributed to differences in procedural details; Copland et al. focused on the unconscious aspects of semantic priming and used short SOA between the prime and the target word (150 ms), which can attenuate the conscious semantic priming effect (e.g., semantic matching or semantic integration processes). In contrast, the present study used relatively long prime-target SOA (600 ms), resulting in the semantic priming effect containing the effect of automatic spreading activation and the effect of semantic matching or semantic integration processes (Hill et al., 2002). Thus, it is

possible that the repetition suppression of the dorsal left inferior frontal gyrus is associated with modulation in several types of semantic processing, such as semantic matching or the semantic integration process, while that of the ventral left inferior frontal gyrus reflects the reduction of demand for retrieval or the selection from semantic knowledge caused by automatic spreading activation. Further investigation to clarify the functional difference of these two regions would be of benefit.

The anterior cingulate cortex also exhibited a significant repetition suppression effect. It has been reported that the anterior cingulate cortex plays an important role in the detection of errors and in behavioral conflict, and is activated under the condition in which response competition occurs (Gehring and Knight, 2000; Kiehl et al., 2000). Thus, increased anterior cingulate activity under the unrelated condition implies that a higher degree of response conflict occurred under the unrelated condition than under the related condition because conscious and unconscious semantic priming can make it easier to make a decision regarding a target word under the related condition.

In the ROI analysis, the left superior temporal gyrus showed significant repetition suppression, and the magnitude of the effect correlated with the magnitude of the N400 priming effect decomposed by ICA across the subjects. Although N400 source is assumed to be mediated by several brain regions (Guillem et al., 1999; Nobre and McCarthy, 1995; Nobre et al., 1994), a number of MEG studies estimated the source of N400 at the bilateral superior temporal gyrus adjacent to the auditory cortex (Helenius et al., 1998, 2002; Laine et al., 2000; Sekiguchi et al., 2001; Simos et al., 1997). Furthermore, several studies have shown that the magnitude of magnetic responses elicited by target words whose source is estimated in the left peri-Sylvian area was reduced by semantic or repetition priming for visual words (Koyama et al., 1999; Sekiguchi et al., 2000, 2001). Thus, the results of present study and those of previous studies suggest that the priming effect observed in N400 is associated with the activity of the superior temporal gyrus.

Neuroimaging studies have reported that the left superior temporal region is activated when subjects perform phonological tasks for visually presented words or letters (Fujimaki et al., 1999; Paulesu et al., 1993; Sergent et al., 1992). Bavelier et al. (1997) showed that this area was more strongly activated by the visually presented phonologically legal pronounceable word than by the phonologically illegal consonant word. Herbster et al. (1997) also reported that the left superior temporal cortex was related to the processing of pronounceable words. Based on these observations, Binder and Price (2001) suggested that the left superior temporal cortex mediates the preservation of the phonological representation of words. Notably, several studies have indicated the that N400 and phonological processing are related. Nobre and McCarthy (1994) reported that N400 was elicited by phonologically legal words but not by phonologically illegal nonwords, indicating that N400 is associated with access to the phonological representation of words. Similar results were reported by Bentin et al. (1999) and Rugg and Nagy (1987). The consistent result with regard to the involvement of N400 response and superior temporal activity in word-related phonological information supports the finding of the present study that the N400 priming effect is correlated with the activity of the superior temporal gyrus. If N400 reflects the activation of the superior temporal cortex, then the N400 priming effect in the present study suggests that semantic priming modifies phonological representation.

Recent behavioral studies emphasize the importance of phonological information in the recognition of visual words. For example, Drieghe and Brysbaert (2002) showed that a target word (e.g., "frog") could be primed not only by an associated word (e.g., "toad") but also by a homophone (e.g., "towed") and pseudohomophone (e.g., "tode") of the associated word, indicating that semantic representations are coded as a word by a phonological lexicon. According to this model, in a semantic priming task, a prime word can activate the semantic representation of the word, and the activation of semantic representation can activate the phonological lexicon that is related to the semantic representation. This would result in easier access to the phonological lexicon of a target word when a subject makes a semantic judgment. If N400 reflects the access to the phonological lexicon of a word, the N400 priming effect in semantic or repetition priming may be mediated by easier access to the phonological lexicon of the target word due to its prior activation by the prime word.

Although the dorsal and ventral part of the left inferior frontal gyrus and the anterior cingulate cortex showed significant repetition suppression, the effect did not correlate with the magnitude of the N400 priming effect from ICA component. This would imply that the activities of these regions are independent of the processing reflected in N400. As discussed above, these regions may be related to retrieval or selection from semantic memory or to response selection or verbal working memory. Selection or working memory activity is associated with the amplitude and latency of the LPC rather than the N400 (Kok, 2001). Thus, activity of the left and right inferior frontal gyrus and anterior cingulate gyrus may be reflected in the LPC. Swick (1998) reported that subjects with lesions in the left inferior frontal cortex showed smaller repetition priming effect on the LPC when compared to control subjects. This result supports the notion that left inferior frontal gyrus activity is associated with the LPC. However, it is difficult to investigate the correlation between the latency or amplitude of LPC and BOLD responses because LPC is a compound component consisting of working memory, episodic memory retrieval, reallocation of cognitive resource, and response selection. Therefore, we could not characterize the relationship between the repetition suppression effect in the inferior frontal gyrus or anterior cingulated cortex and the LPC in the present study. Further investigation to examine the relationship between the LPC and the inferior frontal gyrus or anterior cingulate cortex would be of benefit.

Conclusion

In conclusion, this study provides new evidence that the semantic priming effect on the N400 component is associated with the activity of the left superior temporal cortex. The N400 priming effect decomposed by ICA was correlated with the repetition suppression effect of the BOLD signal caused by semantic priming at the left superior temporal gyrus but not with the BOLD repetition suppression effect of the left inferior frontal gyrus. This result is supported by MEG studies that suggest that the source of N400m is the superior temporal cortex and by neuroimaging studies showing that the left superior temporal gyrus mediates the processing of the phonological representation of words. The present results indicate that the N400 priming effect reflects the modification of the access to the phonological lexicon of words and that the access to the phonological lexicon plays an important role in the semantic priming task.

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