

Lateralized Activation in the Inferior Frontal Cortex during Syntactic Processing: Event-Related Optical Topography Study

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Abstract: Functional imaging with near-infrared light has the potential to provide novel information that cannot be obtained with other imaging techniques. An event-related paradigm has not been fully established for studying human cognitive functions with near-infrared optical imaging. We conducted language experiments to develop an event-related paradigm with optical topography (OT). We directly compared cortical activation during syntactic and semantic decision tasks, both of which involved error detection in a sentence stimulus that consisted of a noun phrase and a verb. In the syntactic decision task, subjects judged whether the presented sentence is syntactically correct, where the syntactic knowledge about the distinction between transitive and intransitive verbs was required. In the semantic decision task, subjects judged whether the presented sentence is semantically correct, where the lexico-semantic knowledge about selectional restrictions was indispensable. We found local increases in oxyhemoglobin concentration, which were selectively associated with the syntactic decision task. Activation in the left inferior frontal gyrus was detected when syntactically anomalous sentences were presented, whereas there was no significant activation in this region when semantically anomalous sentences were presented. Moreover, identical stimuli of normal sentences elicited activation in the left inferior frontal gyrus, only when the employment of syntactic knowledge was required. This task-selective activation was not observed in any other measured regions, including the right homologous region. These results demonstrate that OT techniques, when coupled with the event-related paradigm, are useful for studying the higher cognitive functions of the human cerebral cortex. *Hum. Brain Mapping* 17:89–99, 2002. © 2002 Wiley-Liss, Inc.

Key words: near-infrared spectroscopy; optical topography; functional imaging; hemodynamics; language; syntax; semantics

INTRODUCTION

The light absorption spectra of oxyhemoglobin and deoxyhemoglobin differ in a near-infrared range. The near-infrared spectroscopy (NIRS) techniques have enabled the assessment of hemoglobin concentration changes in brain tissues [Chance et al., 1988; Frostig et al., 1990; Jöbsis, 1977; Villringer et al., 1993]. Based on the same principle, optical topography (OT) was recently developed as a non-invasive technique for functionally mapping the human cerebral cortex [Koizumi et al., 1999; Maki et al., 1995; Yamashita et al., 1996]. A major difference between OT and NIRS is that OT

Contract grant sponsor: Japan Science and Technology Corporation (JST); Contract grant sponsor: Human Frontier Science Program (HFSP).

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Received for publication 12 October 2001; accepted 19 April 2002

DOI 10.1002/hbm.10050

measures spectroscopic reflection and scattering simultaneously from multiple measurement points, whereas NIRS measures these effects with one or a few pairs of a light emitter and a detector. Using OT, we have previously reported focal activation in the left superior temporal cortex, by comparing speech recognition of stories and repeated sentences [Sakai et al., 2001; Sato et al., 1999].

NIRS and OT techniques provide several advantages over other imaging methods. First, these techniques provide independent measurement of the concentration changes in oxy- and deoxyhemoglobin. Second, they produce no instrument noise interfering with the auditory stimuli. Third, they do not require a head constraint; thus their application may enable developmental mapping studies of infants. Previous NIRS and OT studies have investigated the hemodynamic changes associated with various functions such as visual processing [Kato et al., 1993; Villringer et al., 1993] and language processing [Fallgatter et al., 1998; Hock et al., 1997; Sakatani et al., 1998; Watanabe et al., 1998].

All of these studies, however, have used a blocked task paradigm that measures accumulated activation over many trials presented in close succession. Such a procedure does not distinguish individual trials within one block, and thus, an analysis according to individual trial types (e.g., stimulus types or subjects' responses) is not possible. Several recent studies have reported an event-related paradigm using NIRS in the motor and visual areas [Obrig et al., 2000; Wobst et al., 2001]. We combined an event-related experimental design with the OT techniques, and applied it to the study of cortical responses during language processing. The advantages of our OT techniques over previous NIRS studies of language functions are two-fold. By employing an event-related design, stimulus types in each language task, such as normal and anomalous sentences, can be intermixed, making selective averaging according to stimulus types possible. By using OT, we can simultaneously measure cortical responses in a large area, including the frontal and temporal association areas. This is important because higher-level cognitive events like language processing may elicit activity in various cortical regions.

MATERIALS AND METHODS

Subjects

Eight male native Japanese speakers (ages 22–36 years) participated in the present study. They showed right-handedness (laterality quotients: 81–100) by the

Edinburgh inventory [Oldfield, 1971]. Informed consent from each subject was obtained according to the declaration of Helsinki. Approval for the human experiments was obtained from the institutional review board of the University of Tokyo, Graduate School of Arts and Sciences.

Tasks

In the present experiment, subjects were asked to listen to spoken language stimuli and to make linguistic decisions with their eyes closed. Speech sounds presented in the tasks were digitized (16 bit; the normal audio cut-off, 11,025 Hz) using speech synthesis software (Oshaberi-mate, Fujitsu, Tokyo, Japan) that converted Japanese written text into sound waveforms. They were presented with a stereophonic headphone at maximum sound pressure levels of 80 dB.

We compared cortical activation mainly between two explicit linguistic tasks: syntactic decision (Syn) and semantic decision (Sem) tasks (Fig. 1). These tasks were basically error detection in a sentence stimulus: one stimulus of a noun phrase (a noun and a case particle), followed by a verb stimulus for each trial. Each noun phrase and each verb was always three-syllable long and presented for 350 msec to ensure a constant listening time. The same set of words were used to make normal (N) and anomalous (A) sentences for each task. We prepared an original set of 60 pairs of a noun phrase and a verb. One half of the original pairs were used as N stimuli for each task. An additional 30 pairs were made from the original set as A stimuli for each task, by varying noun phrase-verb combinations (Fig. 1A). Thus, each A stimulus of one task was matched for where a single anomaly occurred. These stimuli formed minimal pairs for both intratask pairs (N and A sentences) and intertask pairs (e.g., A sentences for Syn and Sem). We named this novel task design as a minimal-pair paradigm.

In the Syn task, subjects judged whether sentences were either syntactically normal or anomalous, while word combinations in each sentence were semantically related. We focused on a universal aspect of syntactic operations that are common to both English and Japanese: a distinction between transitive verbs (*vt*) and intransitive verbs (*vi*). This distinction is critical in sentence comprehension because the choice of a transitive or intransitive verb determines the syntactic structure of a sentence [Smith and Wilson, 1979]. Subjects were explicitly instructed to detect a syntactic anomaly, but they were not instructed to pay attention to the distinction between *vt* and *vi*. In the Sem task, subjects judged whether sentences were either seman-

A

Task	Stimuli with Acc (を)		Stimuli with Nom (が)
Syntactic decision (Syn)	ゆきを さわる N snow-Acc touch (vt) (Someone) touches snow		ゆきが さわる N snow-Nom touch (vt) Snow touches (something)
	ゆきを つもる A snow-Acc lie (vi) (Someone) lies snow		ゆきが つもる N snow-Nom lie (vi) Snow lies
Semantic decision (Sem)	ゆきを さわる N snow-Acc touch (vt) (Someone) touches snow		ゆきが さわる N snow-Nom touch (vt) Snow touches (something)
	—————		ゆきが つもる N snow-Nom lie (vi) Snow lies
	ゆきを しかる A snow-Acc scold (vt) (Someone) scolds snow		ゆきが しかる A snow-Nom scold (vt) Snow scolds (someone)
	—————		ゆきが にげる A snow-Nom escape (vi) Snow escapes

B

Task	Syntactic relationship between a verb and a noun phrase	Lexico-semantic relationship between a verb and a noun
Syn	Normal / Anomalous	Always correct
Sem	Always correct	Normal / Anomalous

Figure 1.

A: Sentence comprehension tasks that contrast syntactic and semantic processing. In the syntactic decision (Syn) task, participants were asked to distinguish whether a given sentence was syntactically normal (N) or anomalous (A). In a semantic decision (Sem) task, participants were asked to decide whether a given sentence was semantically N or A. In the Syn task, the accusative (Acc) case particle could produce either N or A sentences, depending on whether a transitive verb (vt) or intransitive verb (vi) was used. Stimuli (gray shaded) with the nominative (Nom) case

particle were not used in the Syn task, because they produced only syntactically N sentences. In the Sem task, Acc and Nom produced either N or A sentences, depending on the denotative meaning of the verb used. **B:** The distinction between the Syn and Sem tasks. Distinct types of linguistic processing were required to perform the two tasks correctly. The syntactic knowledge about vt/vi distinction was required for judging Syn N or Syn A, while the lexico-semantic knowledge about selectional restrictions was indispensable for judging Sem N or Sem A.

TABLE I. Behavioral data*

	Syn N	Syn A	Sem N	Sem A	Pitch-match	Pitch-nonmatch
Accuracy (%)	88.9 ± 2.7	93.1 ± 2.8	85.7 ± 2.5	92.4 ± 3.7	97.5 ± 1.9	97.1 ± 1.5
Reaction time (msec)	546 ± 65	593 ± 58	558 ± 79	585 ± 59	390 ± 85	403 ± 68

* Values are expressed as mean ± SE (n = 8 subjects).

tically normal or anomalous, while presented sentences were syntactically correct as to the usage of *vt* and *vi*. We focused on the lexico-semantic relationship (selectional restrictions) between a verb and a noun. For example, ‘snow’ and ‘lie’ (Sem N) are lexico-semanticly associated, whereas ‘snow’ and ‘scold’ or ‘snow’ and ‘escape’ (Sem A) have little association (Fig. 1). This distinction was confirmed by high accuracy in the Sem task (Sem N, 85.7%; Sem A, 92.4%; Table I).

The Syn task cannot be solved on the basis of the lexico-semantic relationship between a verb and a noun, because it is always correct for both Syn N and Syn A. In Syn A, there was an anomaly in the syntactic relationship between a verb and a noun phrase marked for object. Moreover, transitive and intransitive verbs in Japanese are clearly segregated into different words, and there are a number of morphologically related verb pairs (e.g., *tomeru* (*vt*) and *tomaru* (*vi*); gloss: ‘stop’), which are similar to *raise-rise* distinction in English [Tsujiura, 1996]. Although the ambiguity of English verbs (*vt/vi*) like ‘stop’ is resolved by both syntactic (presence/absence of object) and semantic information of a sentence, transitivity of Japanese verbs is primarily determined by morpho-syntax or words per se. Therefore, the Syn task explicitly requires syntactic knowledge for distinguishing transitive and intransitive verbs.

Before the experiments, we explicitly explained the nature of two tasks to the subjects, providing examples for each of Syn A, Sem A, Syn N, and Sem N with the following instruction: “The sentence ‘*yuki-wo tsumoru*’ (snow-Acc lie; Acc, the accusative case particle) is anomalous because of the syntactic violation between a verb and a noun phrase. Because ‘*yuki*’ (snow) and ‘*tsumoru*’ (lie) are lexico-semanticly associated, as ‘*yuki-ga tsumoru*’ (snow-Nom lies; Nom, the nominative case particle) is acceptable, it is not a semantic but a syntactic error. In contrast, the sentence ‘*yuki-wo shikaru*’ (snow-Acc scold) is anomalous because of the lexico-semantic mismatch between ‘*yuki*’ (snow) and ‘*shikaru*’ (scold). Because this sentence is syntactically correct as to the relationship between a verb and a noun phrase, this is not a syntactic but a

semantic error. Finally, the sentence ‘*yuki-wo sawaru*’ (snow-Acc touch) is normal because it is both syntactically and semantically correct.”

Taking the distinctions between the Syn and Sem tasks into account, our task design can be summarized as the scheme shown in Figure 1B. The two tasks explicitly required these distinct task demands. Therefore, the task demands correspond to the different components of sentence processing. Similar task designs have been used in previous fMRI studies [Kang et al., 1999; Ni et al., 2000] for contrasting implicit syntactic and semantic processes. In these studies with English sentences, syntactic anomalies, such as ‘Trees can grow’, and semantic anomalies, such as ‘Trees can eat’ were introduced.

To control for non-linguistic components such as auditory perception of sounds, decision of two choices, and motor responses, we employed a pitch judgment (Pitch) task. In this task, a pair of pure tones (300 Hz or 400 Hz) superimposed in white noises (the low-pass cut-off, 5,512 Hz) was presented for 350 msec for each tone, and subjects judged whether the pair was at the same pitch (Match) or different pitches (Nonmatch).

During the experiments, the three tasks were conducted in separate runs. Before each run, the subjects were explicitly informed about which task they should have performed. In the Syn task, we instructed: “Press the green button if the presented sentence is syntactically correct; press the red button if it is syntactically incorrect.” In the Sem task, we instructed: “Press the green button if the presented sentence is semantically correct; press the red button if it is semantically incorrect.” In the Pitch task, we instructed: “Press the green button if the pair is at the same pitch; press the red button if it is at different pitches.” A single run contained ten trial events, with variable inter-trial intervals (20, 22, 24, 26, and 28 sec, pseudo-randomized within a run). Our event-related design corresponds to a single-event study, in which single, well-separated events were analyzed. The order of N/A or Match/Nonmatch stimuli was pseudo-randomized in each run, and the number of presentations of N/A or Match/Nonmatch stimuli was equated in each task.

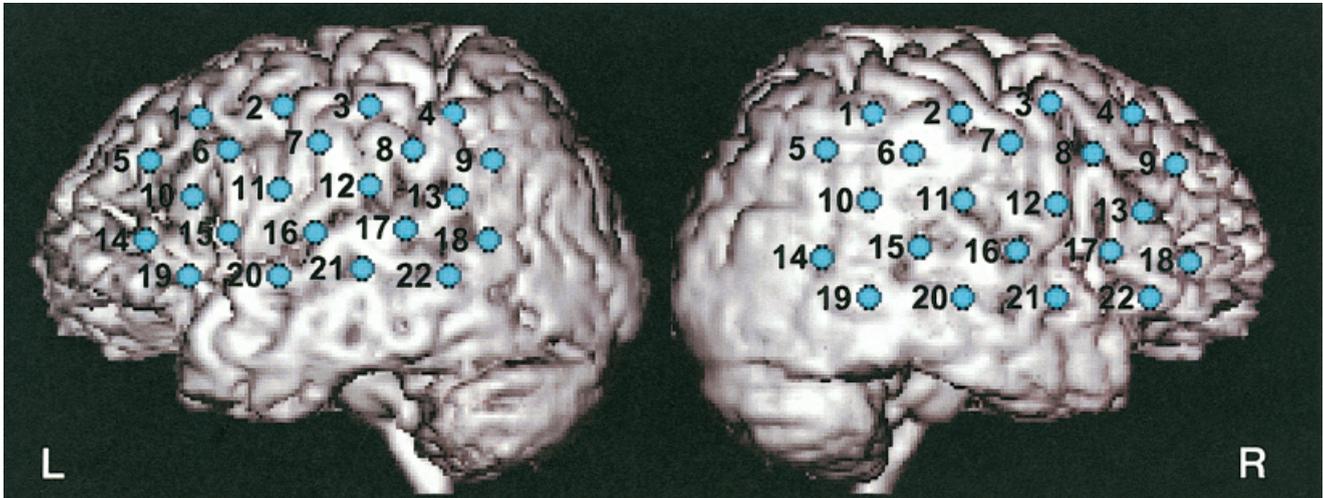


Figure 2.

The measurement points in the present OT experiment. Images of the left lateral surface (L) and the right lateral surface (R) are shown. The cortical surface image was reconstructed from 3D MR

images of a representative subject, and measurement points were superimposed onto the cortical surface image. The numbers denote channel numbers of the measurement points.

During the scanning, both accuracy and RT were measured on line [Hashimoto et al., 2000]. As a baseline, subjects were asked to attend to a continuous tone (400 Hz) until the next stimulus was presented. There were 12 runs in one imaging session (four runs for each task) and the orders of tasks were counterbalanced. Each subject was tested in two sessions.

Optical topography measurements

We used two OT systems (ETG-100 and ETG-A1; Hitachi Medical Corporation, Tokyo, Japan), one for each hemisphere. Near-infrared laser diodes with two wavelengths (ranges: 782–793 and 823–833 nm) were used as the light sources (maximum intensity: 2 mW/mm², intensity modulation: 1–10 kHz). The reflected lights were detected with avalanche photodiodes located 30 mm from an emitter. In each hemisphere, eight emitters and seven detectors were alternately placed on a head shell at square intersection points of a 3 × 5 grid. This configuration formed 22 pairs of optic probes, or 22 channels, each of which consisted of a detector and one of adjacent emitters. Optical signals from multiple emitters with independently modulated laser intensities were separated by rock-in amplifiers without cross talk between the signals [Yamashita et al., 1999]. Forty-four channels in both hemispheres were simultaneously recorded every 500 msec to obtain the transmittance data $\ln T(\lambda, t)$ as a function of wavelength (λ) and a measurement time (t). The measured region centered on the Sylvian fissures and

covered an area of 6 × 12 cm² in each hemisphere (Fig. 2).

Data analyses

We extracted 10 event periods from time-series data of $\ln T(\lambda, t)$ in a single run, allowing for overlaps during the baseline. Each event period ranged from 6 sec before the stimulus onset to 20 sec after the onset. Excluding the activation period during 12 sec after the stimulus onset [Ni et al., 2000], time points were baseline-corrected with a curve of the third degree [Sato et al., 1999]. For each session, the event data of six conditions (Syn N, Syn A, Sem N, Sem A, Pitch-Match, and Pitch-Nonmatch) were averaged separately at each wavelength. Only the trials in which subjects had responded correctly were incorporated to the averaging. After averaging, the relative changes in oxyhemoglobin concentration (C_{oxy}) and deoxyhemoglobin concentration (C_{deoxy}) were calculated [Maki et al., 1995].

For a group analysis, we averaged the data in each corresponding channel across subjects. The hemoglobin time points of C_{oxy} in Pitch-Match and Pitch-Nonmatch were averaged together for control responses. Then we subtracted the averaged control responses from C_{oxy} changes in one of four language conditions. We calculated correlation coefficients (r -values) between these subtracted data and a basis function of the peri-stimulus time for hemodynamics [Friston et al., 1998a]. This subtraction method was

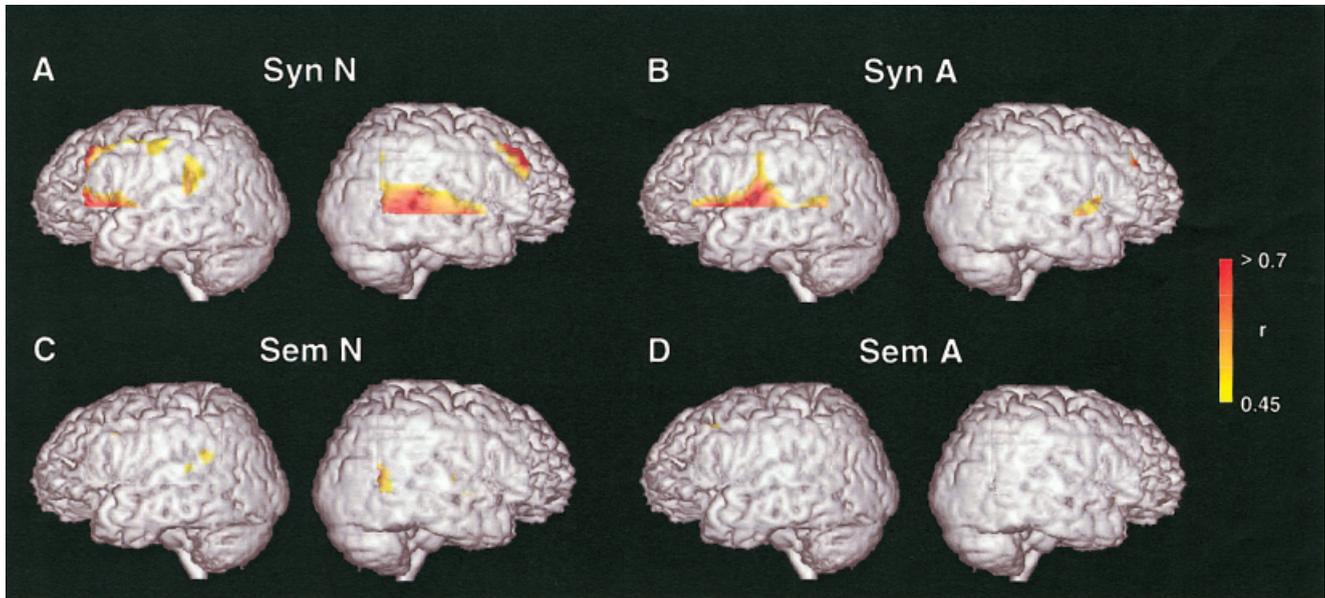


Figure 3.

Oxyhemoglobin *r*-maps under four language conditions compared to a pitch judgment task: Syn N (**A**), Syn A (**B**), Sem N (**C**), and Sem A (**D**). In each *r*-map, *r*-values at the measurement points

were used for linear interpolation, and then *r*-values at intermediate voxels were bilinearly interpolated and color-coded, as shown by a color bar at the right.

based on the assumption that hemodynamic responses in each task condition are proportional to the basis function [Boynton et al., 1996; Cohen, 1997]. Therefore, the subtracted time-series is considered to be also proportional to the basis function. A threshold of *r*-values for statistical significance was set to 0.45 (time points, $N = 52$; $P = 0.05$), based on an equation in a previous study [Bandettini et al., 1993], thereby taking into account the multiple comparisons (44 channels in both hemispheres).

Image reconstruction

After each session, a 3D magnetic resonance (MR) image was obtained to precisely determine anatomical positions of the channels. Alfalcidol beads ($0.25 \mu\text{g}$) buried in the head shells were used as MR markers, which can be identified on the MR image as spheres (diameter: 3 mm). Each MR marker was located at the midpoint between an emitter and a detector. The MR marker points were projected onto the cortical surface

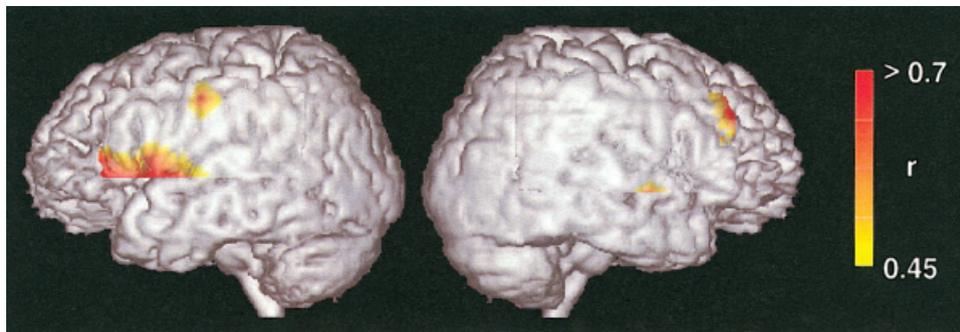


Figure 4.

Localized activation in the left inferior frontal gyrus, selectively associated with the Syn task. Oxyhemoglobin *r*-maps of Syn–Sem are shown on the lateral surface images. Note the prominent activation in the left inferior frontal gyrus at left channels 14, 15, and 19 (*r*-values: 0.73, 0.68, and 0.69, respectively). We made the

same comparison using deoxyhemoglobin data; this region did not show significant correlations at these left channels (*r*-values: 0.34, -0.11 , and 0.30, respectively). The corresponding right channels 17, 18, and 22 showed little activation for oxyhemoglobin data (*r*-values: 0.25, 0.35, and 0.10, respectively).

image as follows, using custom-made software for image reconstruction (K.G.T., Tokyo, Japan). First, a curved surface was obtained for each hemisphere by a spline interpolation of the 3D positions of 22 MR markers. Next, the curved surface was projected to the extracted cortical surface image of the same subject, perpendicularly to the curved surface. A measurement point was defined as an intersection of the cortical surface image and the perpendicular line from a marker point, which corresponds to the anatomical position of each channel. These procedures conformed to the assumption that optical signal changes are maximum at the measurement points, as shown by the spatial distribution of regionally averaged photon-path length calculated from stored photon paths [Maki et al., 1996]. Using these procedures for each session, we confirmed that the three measurement points of left channels 14, 15, and 19 were within the left inferior frontal gyrus (see Fig. 2).

In Figures 3 and 4, r -maps for averaged data across subjects were superimposed on cortical surface images of a representative subject. For this image reconstruction with the same software mentioned above, r -values at the measurement points were used for linear interpolation to make a 5×9 grid at spatial intervals of 15 mm, and then r -values at voxels within each square area were bilinearly interpolated and color-coded to obtain an entire r -map on the cortical surface image.

RESULTS

Behavioral accuracy and reaction time measured from the onset of a latter stimulus are shown in Table I. An ANOVA indicated a significant main effect of task as regards both accuracy and reaction time (accuracy: $F(2,45) = 5.3, P < 0.01$, reaction time: $F(2, 45) = 33.6, P < 0.0001$). Post-hoc tests (Fisher's PLSD) showed a difference between Syn and Pitch (accuracy: $P < 0.05$, reaction time: $P < 0.0001$), and between Sem and Pitch (accuracy: $P < 0.01$, reaction time: $P < 0.0001$). The difference between Syn and Sem, however, was not significant (accuracy: $P > 0.1$, reaction time: $P > 0.5$). These results suggest that Syn and Sem tasks were equally balanced for task difficulty in terms of behavioral control. To examine the effect of stimuli (N or A), another two-way ANOVA was performed: task (Syn, Sem) \times stimulus (N, A). Main effects and the interaction were not significant both in accuracy and reaction time ($P > 0.05$ for all).

Figure 3 shows the r -maps for C_{oxy} changes in the four language conditions. In Syn N, there was signif-

icant activation in the left inferior frontal gyrus (L. IFG), the bilateral middle frontal gyrus, and the right superior temporal cortex. The left supramarginal gyrus was also activated, although its activity was relatively weak. In Syn A, L. IFG as well as the right middle frontal gyrus and the right superior temporal gyrus showed similar activation, whereas additional activation was observed in the left superior temporal cortex. In Sem N and Sem A, activation was much weaker than in Syn N and Syn A. The left supramarginal gyrus and the right middle temporal gyrus were weakly activated only in Sem N.

To show regions reflecting a difference between the Syn and Sem tasks, we directly compared Syn responses (averaged data for Syn N and Syn A) and Sem responses (averaged data for Sem N and Sem A), as shown in oxyhemoglobin r -maps of Syn–Sem (Fig. 4). The most significant difference was observed in L. IFG, spreading among the three measurement points of left channels 14, 15, and 19. We averaged the data of these three points and calculated the time-series of C_{oxy} in each of four language conditions (Fig. 5A, B). Event-related increases of C_{oxy} were clearly observed in Syn N and Syn A (Fig. 5A; $r = 0.83$ and 0.66 , respectively), while they were observed neither in Sem N nor in Sem A (Fig. 5B; $r = 0.02$ and -0.35 , respectively). We further calculated the mean C_{oxy} changes in this region, using temporal points from 3–9 sec after the stimulus onset (Fig. 5C). A two-way ANOVA (task \times stimulus) indicated the significant main effect of task ($F(1, 28) = 5.3, P < 0.05$), but without the main effect of stimulus and the interaction ($P > 0.5$). Finally, we confirmed that the subtracted data indeed followed the basis function. The subtracted time-series in Figure 5D (blue line) showed a high coefficient of determination ($r^2 = 0.63$) for fitting the data with the basis function (orange line).

In contrast, the right hemisphere did not show this Syn-selective activation. Figure 5E and F showed the time-series of C_{oxy} in the right homologous region (R. IFG) at right channels 17, 18, and 22. There was no significant C_{oxy} change in any of the four conditions (r -values; Syn N: 0.24, Syn A: 0.05, Sem N: 0.05, Sem A: -0.33), and an ANOVA indicated no significant main effects or the interaction among the mean C_{oxy} changes (Fig. 5G; $P > 0.5$). The coefficient of determination for fitting with a hemodynamic response function in the right IFG was much lower ($r^2 = 0.11$) than that in L. IFG (Fig. 5H). We performed two-way ANOVA at other channels, but neither significant main effects nor interactions were observed ($P > 0.05$ for all). These results confirmed the left-lateralized

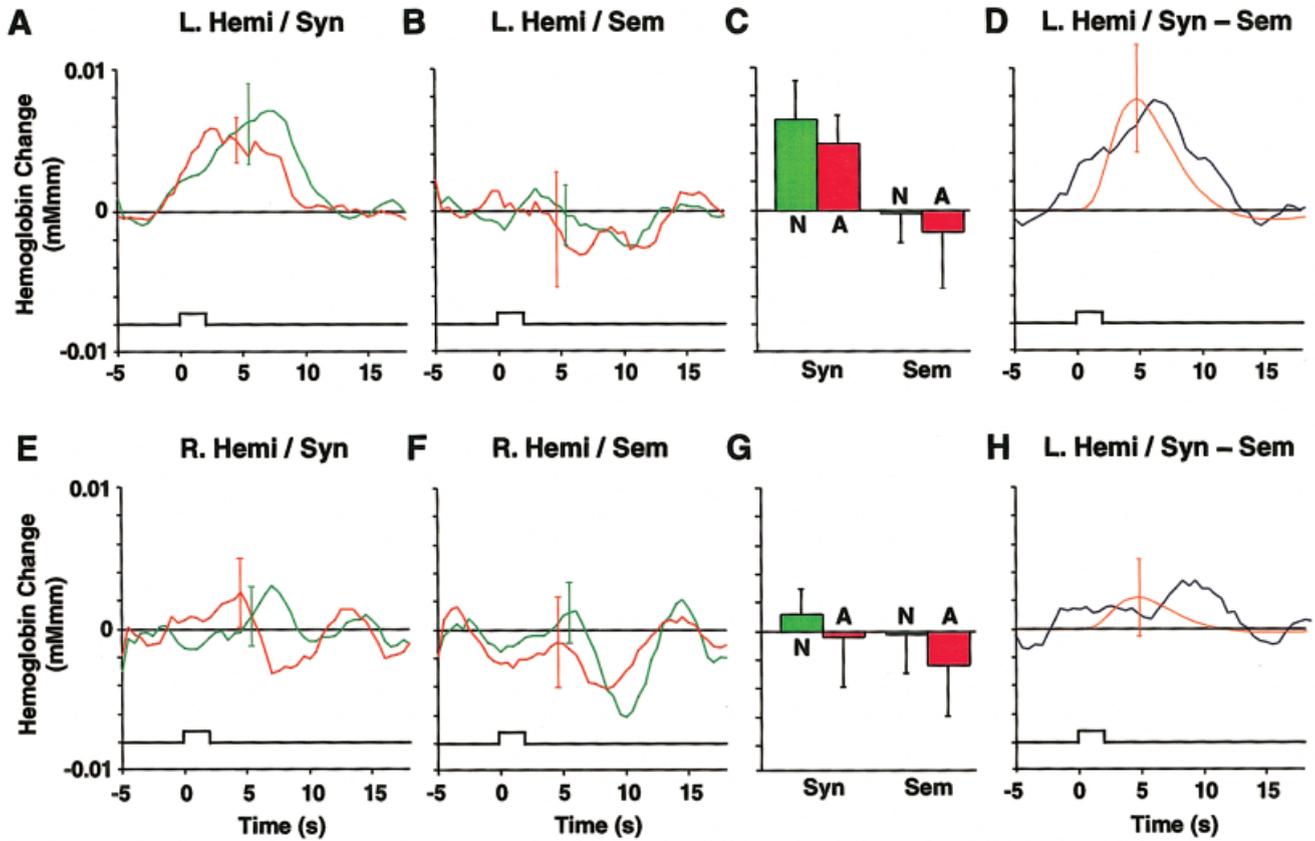


Figure 5.

Event-related hemodynamic changes in the left and the right inferior frontal gyrus. **A,B:** C_{oxy} time-series in Syn (A) and Sem (B) tasks, averaged across three measurement points in the left inferior frontal gyrus. Hemodynamics for normal (green) and anomalous (red) sentences were plotted in each panel. Sentence stimuli were presented at time zero, and responses were completed in 2 sec (events chart). The vertical axis represents relative hemoglobin changes (mMmm), which are the values of hemoglobin concentration (mM) multiplied by the effective path length in brain tissues (mm). For display purposes, data points were smoothed using a five-point moving average. Error bars indicate standard

errors of the mean (SE) across eight subjects. **C:** Mean C_{oxy} changes of the four language conditions in (A) and (B). Error bars indicate SE across the subjects ($N = 8$). **D:** A differential hemodynamic response between Syn and Sem in the left inferior frontal gyrus. The averaged time-series of Sem N and Sem A was subtracted from the averaged time-series of Syn N and Syn A. The subtracted time-series (blue line) were fitted to the basis function (orange line) with a least square method. Error bars indicate SE across the subjects. **E-H:** C_{oxy} time-series, mean C_{oxy} changes, and subtracted time-series in the right inferior frontal gyrus, using the same format as that in (A-D).

and localized activation of the inferior frontal gyrus when the Syn task was performed.

DISCUSSION

In the present study, we demonstrated that an event-related paradigm with OT techniques was sufficiently sensitive to investigate linguistic processes in the human brain. We directly compared cortical activation during syntactic and semantic tasks and demonstrated task-selective C_{oxy} changes in L. IFG, which were highly lateralized to the left hemisphere. Furthermore, this region was activated in Syn N and Syn

A, both of which required syntactic processing. Because stimuli in Syn N and Sem N were physically identical, differential activation patterns between Syn N and Sem N may reflect distinct linguistic factors required in the Syn and Sem tasks. Therefore, our novel language paradigm with strict linguistic controls, used together with event-related OT techniques, unequivocally showed specific cortical activation in sentence processing.

We found differential activity during the Syn task between L. IFG and R. IFG; significant C_{oxy} increases associated with the Syn task were observed only in L. IFG. These results are consistent with previous func-

tional imaging studies [Dapretto and Bookheimer, 1999; Kang et al., 1999], which reported selective activation in a part of L. IFG during implicit syntactic vs. semantic processing of sentences or phrases. Our previous fMRI study also showed that L. IFG is critically involved in explicit syntactic processing [Embick et al., 2000]. In the present study, increased C_{oxy} changes in L. IFG may reflect not just syntactic processing but the difference between it and semantic processing. It should be noted that the comparisons of both Sem N vs. Pitch and Sem A vs. Pitch showed no significant difference in L. IFG (Fig. 3C,D), suggesting that the semantic processing have no effect on the activation in L. IFG. Therefore, as to L. IFG activation, the effect of the difference between syntactic and semantic processing becomes equivalent to that of the syntactic processing alone.

The sentences in Syn A had intransitive verbs that were accompanied by nouns case-marked for object (intransitivity violations). Because meaning of a sentence is derived from syntactic analyses of the sentence structure, the sentences in Syn A become semantically impossible. This type of semantic anomalies stems from intransitivity violations imposed in the Syn task, and thus it is indirect or secondary anomaly, which should be conceptually distinguished from the primary anomaly in the Syn task. It was not known whether the subjects explicitly made their decisions on the basis of the characteristics of the stimuli. The subjects could have based their decisions on the secondary anomaly in sentences. Nevertheless, the semantic anomalies created by intransitivity violations in the Syn task are qualitatively different from the semantic anomalies created by selectional restriction violations in the Sem task. Moreover, the semantic anomalies in the Syn task are all-or-none type, because intransitivity violations can be present or not in sentences. In contrast, the range of anomalies in the Sem task is continuous, as it corresponds to the acceptability of word-to-word associations. Therefore, semantic anomalies in the two tasks are quantitatively different as well. We cannot rule out entirely the possibility that the oxygenation effects in L. IFG reflected the semantic anomalies in the Syn task. On the other hand, previous imaging studies have accumulated evidence that L. IFG is involved in syntactic processing [Friederici et al., 2000; Indefrey et al., 2001; Moro et al., 2001]. In these studies, Jabberwocky sentences were used, in which all content words were replaced with pseudowords while inflections and function words were maintained to preserve syntactic structures. Without any contribution of semantic factors, activation in the left pars opercularis [Friederici et al., 2000]

and in the left pars triangularis [Moro et al., 2001] was observed during syntactic judgments. Indefrey et al. [2001] also reported activations around the left inferior frontal sulcus, which may correspond to the activation of the left middle frontal gyrus in Syn N. These results indicate that activations in L. IFG and its adjacent area are closely related to syntactic processing, suggesting that L. IFG activation in the present study may be due to syntactic processing of sentence structures.

The validity of the subtraction method we employed was confirmed by the high coefficient of determination for fitting the C_{oxy} data in L. IFG with the basis function, indicating that the time-series difference between Syn and Sem was proportional to the basis function. Moreover, given the low frequency of word presentation in the present study (mean in a single run: 5 words/min), the nonlinear second-order component of the hemodynamic response function can be regarded as negligible [Friston et al., 1998b]. We also confirmed that our results were robust and did not depend on the shape of a hemodynamic function. Calculating a correlation between the subtracted time-series and a box-car waveform (duration: 3–8 sec after the onset of a former stimulus, full-width half-maximum of standard hemodynamics), the resultant r -map was almost identical with Figure 4.

Previous event-related fMRI studies have identified activation in L. IFG when syntactically anomalous as opposed to normal sentences were presented [Kang et al., 1999; Ni et al., 2000]. In the present study, however, L. IFG was activated both in Syn N and Syn A, and C_{oxy} changes in these two conditions did not show a significant difference (Fig. 5A,C). Previous studies have used implicit or passive tasks for both syntactic and semantic conditions, and these task designs lack a control for the apparent attention to syntactic/semantic processing and difference involved. The present task differed from previous ones in controlling for deployment of attention to the nature of the anomaly, as ensured by the following three procedures. First, we explicitly explained the nature of the two tasks to the subjects before the experiments (see Materials and Methods). Second, there were two distinct task demands for linguistic knowledge: the syntactic knowledge about *vt/vi* distinction in the Syn task, and the lexico-semantic knowledge about selectional restrictions in the Sem task (Fig. 1B). Third, the two tasks were conducted in separate runs, and before each run, we explicitly informed the subjects about which task they should perform. Because of these three procedures, the explicit task demands directed attention either to syntactic processing or to semantic processing, even if the sentences used for Syn N and

Sem N are physically identical. Our results of L. IFG activation are consistent with this differentiation. In contrast to previous studies reporting L. IFG activation induced by syntactic anomalies, the present results suggest that the activation is not due to the presence or absence of a syntactic anomaly, but due to syntactic processing per se required in both Syn N and Syn A.

CONCLUSIONS

The present study demonstrates that an event-related paradigm with OT techniques is useful in studying human cognitive functions. We found the task-selective activation that was localized in L. IFG. To obtain such a spatial information is one advantage of our techniques, which cannot be achieved by the previous NIRS studies. Furthermore, by using the event-related paradigm, we were able to analyze two kinds of stimuli (N and A) separately in each task. Consequently, this paradigm provided the novel finding, such that the physically identical stimuli used for Syn N and Sem N induced the differential activation in L. IFG. Although we were not able to separate primary syntactic factors and secondary semantic factors within the Syn task from the oxygenation effects in L. IFG, it is noteworthy that the present study successfully dissociated different linguistic processes in the Syn and Sem tasks, whereas previous NIRS or OT studies have compared linguistic and non-linguistic processes. A strict comparison among cognitive factors, such as that of subcomponents of sentence processing, was possible in our minimal-pair paradigm. From the several advantages of OT techniques (see Introduction), it is clear that optical imaging has the potential to provide novel information not obtained previously with other imaging methods. Because event-related fMRI paradigms have been successfully applied for neuroimaging of various cognitive functions, the event-related OT techniques developed here would introduce new possibilities for understanding functional aspects of the human cerebral cortex.

ACKNOWLEDGMENTS

We thank Dr. H. Koizumi and Dr. A. Maki for technical advice on OT; Dr. N. Yahata for comments on the manuscript; Mr. R. Hashimoto, Mr. F. Homae, Mr. K. Suzuki, and Mr. Y. Hashimoto for their technical assistance; and Ms. H. Matsuda for her administrative assistance. This work was supported in part by a CREST grant from JST (K.L.S.) and by Young Investigators' Grants from HFSP (K.L.S.).

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