[Title]

Network hyperexcitability in a patient with partial reading epilepsy: Converging evidence from magnetoencephalography, diffusion tractography, and functional magnetic resonance imaging

[Author names and affiliations]

Tomoyuki Fumuro[a,b], Riki Matsumoto[a,*], Akihiro Shimotake[a,c], Masao Matsuhashi[b,d], Morito Inouchi[c,e], Shin-ichi Urayama[d], Nobukatsu Sawamoto[c], Hidenao Fukuyama[d], Ryosuke Takahashi[c], Akio Ikeda[a,*]

[a]Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

[b]Research and Educational Unit of Leaders for Integrated Medical System

54 Shogoin- kawaracho, Sakyo-ku, Kyoto, 606-8507, Japan

[c]Department of Neurology, Kyoto University Graduate School of Medicine

54 Shogoin-kawaharacho, Sakyo-ku Kyoto, 606-8507, Japan

[d]Department of Human Brain Research Center, Kyoto University Graduate School of Medicine, Japan

[e]Department of Respiratory Care and Sleep Control Medicine, Kyoto University Graduate School of Medicine

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

[*Corresponding authors]

Riki Matsumoto M.D., Ph.D.
Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan
Tel: (+81)-75-751-3662, Fax: (+81)-75-751-3663,
Email: matsumot@kuhp.kyoto-u.ac.jp
&
Akio Ikeda M.D., Ph.D.
Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan
Tel: (+81)-75-751-3662, Fax: (+81)-75-751-3663,
Email: akio@kuhp.kyoto-u.ac.jp

[Present address]
The present address is the same as the above one in corresponding authors.

Number of references 26; Number of figures 3; Number of tables 0;
Abstract words 269; Keywords 6;

Highlights

► By means of multimodal investigations, we delineated the spatial-temporal characteristics of reading-induced epileptic spikes in a patient with partial reading epilepsy.

► Katakana reading induced epileptic activation of the left posterior basal temporal area.

► Given hyperexcitability in the whole left fronto-temporal network normally recruited for reading, prolonged reading may result in epileptiform discharges and clinical seizures.

Keywords

Reading Epilepsy

Katakana

Magnetoencephalography

Diffusion tractography

Functional magnetic resonance imaging

Japanese

Abstract

OBJECTIVE:

The pathophysiological mechanisms of partial reading epilepsy are still unclear. We delineated the spatial-temporal characteristics of reading-induced epileptic spikes and hemodynamic activation in a patient with partial reading epilepsy.

METHODS:

MEG was recorded during silent letter-by-letter reading, and the source of reading-induced spikes was estimated using equivalent current dipole (ECD) analysis. Diffusion tractography was employed to determine if the white matter pathway connected spike initiation and termination sites. FMRI was employed to determine the spatial pattern of hemodynamic activation elicited by reading.

RESULTS:

In 91 spike events, ECDs were clustered in the left posterior basal temporal area (pBTA) during Katakana reading. In 8 of these 91 events, when the patient continued to read > 30 min, another ECD cluster appeared in the left ventral precentral gyrus/frontal operculum with a time-difference of ~24 ms. Probabilistic diffusion tractography revealed that the long segment of the arcuate fasciculus connected these two regions. FMRI conjunction analysis indicated that both Katakana and Kanji reading activated the left pBTA, but Katakana activated the left lateral frontal areas more extensively than Kanji.

CONCLUSIONS:

Prolonged reading of Katakana induced hyper-activation of the cortical network involved in normal language function, concurrently serving as the seizure onset and symptomatogenic zones.

SIGNIFICANCE:

Reflex epilepsy is believed to result from intrinsic hyper-excitability in the cortical regions recruited during behavioral states that trigger seizures. Our case shows that reading epilepsy can arise from a hyperexcitable network of cortical regions. Physiological activation of this network can have cumulative effects, resulting in greater reciprocal network propagation and electroclinical seizures. These effects, in turn, may give insights into the brain networks recruited by reading.

1. Introduction

Reading epilepsy (RE) is a type of reflex epilepsy triggered by reading and usually does not involve spontaneous seizures. RE is the only reflex epilepsy classified as an idiopathic localization-related epilepsy syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), but the heterogeneity of previously published observations makes this classification debatable. The current proposed diagnostic scheme defines it as a reflex epilepsy syndrome without specifying a generalized or focal subtype (Engel, International League Against Epilepsy (ILAE), 2001).

Based on previous reports of patients with seizures provoked by reading, 2 types of RE were identified (Koutroumanidis et al., 1998): myoclonic RE and partial RE. The former is characterized by myoclonic jerks of jaw without alexia at seizure onset and bilateral spikes on electroencephalography (EEG). The latter is rare and characterized by ictal alexia associated with a left posterior temporal ictal discharge.

The mechanism proposed to explain triggering of myoclonic RE in reading is the existence of the interaction between a hyperexcitable cortical focus and a cortico-reticular loop (Radhakrishnan et al., 1995). Functional imaging studies have also revealed the hyperexcitability within cortical and subcortical structures (e.g., bilateral globus pallidus, left striatum, and thalamus) (Archer et al., 2003; Salek-Haddadi et al., 2009; Vaudano et al., 2012). Conversely, the mechanism of partial RE in reading is thought to be local cortical hyperexcitability over the left posterior temporal area. This rare symptom has been described previously in a few patients with RE, but the mechanism remains elusive (Wolf, 1994; Radhakrishnan et al., 1995; Koutroumanidis et al., 1998; Maillard et al., 2010).

The Japanese writing system has 2 distinct orthographies, Kanji (morphograms) and Kana (syllabograms). Kanji characters are visual figures strongly associated with semantics; thus, their pronunciations depend on the context in which they appear. Kana is composed of phonological entities that are somewhat comparable with the alphabets in European languages. Kana orthography employs 2 visually distinct syllabaries called Hiragana and Katakana; the former is usually used in combination with a Kanji and the latter is used to write loanwords from European languages. Hiragana and Katakana share the same lexical representations and syllabary despite different shapes.

Here we described a patient with partial RE provoked by reading Katakana characters, but not by Kanji or Hiragana characters. A combination of different noninvasive brain studies were used in the present study: magnetoencephalography (MEG), which detects the dynamic propagation of epileptic spikes, diffusion tensor imaging (DTI) fiber tractography, which is a direct method for depicting the structural connectivity of brain network, and functional magnetic resonance imaging (fMRI), which helps visualize the spatial patterns of neural activity (within cortical and subcortical areas) involved in reading.

The main purpose of this report was, in this rare case, to delineate mechanisms of seizure precipitation and propagation from the viewpoints of system network hyperexcitability. We also investigated the relationship between source localization of epileptic spikes and normal functions of the reading process.

2. Materials and methods

2.1. Case presentation

A 28-year-old right-handed male had a history of infrequent generalized tonic-clonic seizures (GTCS) in the last 13 years. The first GTCS occurred at the age of 15 years when the patient was at rest. Since then, 7 seizures were provoked by Katakana reading. The patient described himself as follows. While reading Japanese sentences comprising Katakana letters, such as while looking for a particular movie title or music for several minutes in the movie rental shop, he became unable to read smoothly or understand the meaning of words of Katakana. When he made efforts to finish reading, his cheeks became stiff and seizures occurred with loss of consciousness.

The brain MRI scan was normal. Prolonged video-EEG monitoring showed the normal posterior dominant rhythm of 10–11 Hz and no epileptic spikes at rest or while asleep. Spikes appeared in the left parieto-temporal area (maximum at P3 ≧ T5, C3, frequency of ~1/20-30 s) 5 min after the patient continuously read Katakana strings letter-by-letter, and not Kanji and Hiragana strings. After 27 min of Katakana reading, he felt the aura and stopped reading. During the aura, ictal EEG showed more frequent spikes (5/10 s) in the same spatial distribution. The spikes disappeared shortly after the reading was stopped. No motor manifestations or other behavioral changes were associated with spikes on video-EEG. On the other hand, paragraph reading (containing

Kanji, Katakana, and Hiragana) did not provoke any spikes. Finding of specific Hangul words from random-aligned Hangul letters did not elicit any spikes either, where the patient had no experience of Hangul scripts reading. Hangul is comparable with the alphabets in European languages.

2.2. MEG, EEG, and MRI acquisition

MEG examination was performed for the spike foci. Informed consent was obtained from him. MEG was recorded with a 306-channel whole-head MEG system (Neuromag, Helsinki, Finland) in a magnetically shielded chamber. EEG was simultaneously obtained using 21 scalp electrodes according to the International 10–20 system. The sampling rate was 1500 Hz. MEG and EEG data were digitally filtered at a bandpass width of 0.1–400 Hz. MRI scans were performed after MEG acquisition. Diffusion-weighted images (DWI), fMRI, and a T1-weighted anatomical image were acquired on a 3-Tesla Trio scanner (Siemens, Erlangen, Germany). The parameters of DWI, fMRI, a T1-weighted image, and the dual-gradient field map have been reported previously (Oguri et al., 2013).

2.3. Reading tasks during MEG recording

During MEG recording, the patient performed a set of tasks: the patient sat in a chair placed approximately 100 inches from a computer screen. The tasks were designed to simulate the situation where he had provoked seizures during reading many Katakana titles/names on the CD or DVD covers in the rental shop. The screen showed strings of 600‐800 letters of Katakana. These were essentially randomized strings without any association, and among them, several meaningful words (e.g., foreign singer's names) were intermixed on a page screen (Fig. 1). The words employed as test materials were highly common in daily life. We instructed the patient to read every letter from left to right in each line covertly. The patient read lines from the top to the bottom of a page. The patient was asked to identify real words among the strings and speak loudly to the examiner once he read over the strings of letters on the screen. It made the patient carefully read each Katakana letter on the screen. As controls, the same tasks were performed with Kanji or Hiragana. As another control, the task of finding specific strings among random-aligned marks was performed. 1 session consisted of 1 page of a screen with Hiragana, Kanji, or marks. Only the Katakana task was repeated for 10 pages of screen in a session. Each session was repeated twice. The patient performed each task randomly in the following order: (1) Hiragana, (2) Kanji, (3) Katakana, (4) break, (5) mark, (6) Kanji, (7) mark, (8) Katakana, and (9) Hiragana.

2.4. Generator sources of MEG spikes

MEG spikes provoked by the aforementioned Katakana reading and control tasks were visually inspected. Equivalent current dipoles (ECDs) were calculated for spikes using a single sphere model. We followed the analysis procedure described previously (Enatsu et al., 2008). In order to better delineate the anatomical localization of ECDs, ECDs identified on the T1 volume acquisition (3T, MPRAGE) were non-linearly co-registered to the Montreal Neurological Institute (MNI) standard space (ICBM-152) using FNIRT of the FSL version 4.1.2 software (www.fmrib.ox.ac.uk/fsl/fnirt/). This method has been reported elsewhere for standardization of electrode locations (Matsumoto et al., 2012).

2.5. Diffusion tractography

For tractography, we employed DWI data to trace the patient's white matter pathway between the 2 regions shown by clustered ECDs in the MEG study. Probabilistic diffusion tractography was performed on the basis of the 2 regions of interest (ROIs)-based approach. The details of this method have been reported previously (Oguri et al., 2013). For the seed and target points, each ROI was drawn as a sphere located in averaged coordinates of clustered ECDs, as in a previous study (Kamada et al., 2007). In order to exclude the error course, such as the tracts into the contralateral hemisphere or the cortico-spinal tract, exclusion ROIs were obtained at the cerebrospinal fluid and midline. One ROI was set as a seed image and the other was waypoint and termination mask. This procedure was conducted in both directions between the 2 ROIs. The results for each track were combined and thresholded at 10% of the maximum connectivity value. Next, the tract was binarized and smoothened with a 1-mm full-width half maximum Gaussian kernel for 3D display in the patient's MPRAGE.

2.6. FMRI

Three types of visual stimuli such as (i) Katakana (4 characters), (ii) Kanji (2 characters), and (iii) the control script (Tibetan, 2 characters totally different from Kana or Kanji) were displayed. To equate the retinal image size of the stimuli among every script form, we placed an asterisk (*) at the beginning and the end of each Kanji word and Tibetan scripts. Katakana and Kanji words were matched for sound and meaning. Familiarity values of all employed words were high, being above 5.00 according to the 7-point rating scale in Japanese (Amano and Kondo, 1999). After the removal of any possible characters resembling the Katakana and Kanji characters used in the present study, Tibetan script was used as the control script. Since the patient had not learnt Tibetan, the letter strings of this language were completely unfamiliar and provided no linguistic information (i.e., word sound and word meaning).

The block design was done with alternating 24-s task blocks and 3-s rest blocks. In each task block, a small fixation cross mark appeared at the center of the visual display, and 16 words were presented at a rate of 1/1.5 s, with 300 msec of display duration followed by 1200-msec blank period. Sixteen consecutive words in 1 task block belonged to the same category of each script. Each script condition was executed in the order of Katakana, Kanji, and the control script. During the rest blocks, only the fixation cross appeared on the screen. This procedure was repeated 4 times with a rest intersession of about 1–2 min. The patient was instructed to fix his gaze at the center of the screen in each trial. In the Katakana and Kanji blocks, he covertly repeated each word in his mind, and pressed the button using his right index finger when the shown words were judged as food names. In the Tibetan block, he pressed the button when the same 2 letters appeared serially. Within each block of 16 words, there were 3 to 5 occasions on which the patient had to respond.

Before fMRI recording, he had a test run outside the scanner to ensure that task words were familiar to him and that no EEG spikes were induced by the task. To prevent word-specific practice effects, the task words in the test run were entirely different from those used in the real fMRI recording. Hangul scripts were used as the control in the test run.

Statistical analyses of his performance in terms of the accuracy and reaction time across each script condition were performed with SPSS (version 15.0j, SPSS Inc., Chicago, Illinois, USA). The regional blood oxygen level dependent (BOLD) effect images were co-registered into his MPRAGE. All imaging procedures and statistical analyses were completed using the FSL and SPM version 8 software (Welcome Department of Cognitive Neurology, London, UK). We conducted subtraction analysis between Katakana and control, and between Kanji and control. Conjunction analysis was performed by combining the 2 subtraction data. The subtraction between Katakana and Kanji was aimed to identify the activated regions associated with the Katakana or Kanji effect. The subsets of voxels exceeding a threshold of $P < 0.001$ ($Z > 3.11$) without correction for multiple comparison were considered to be significant.

3. Results

3.1. Spikes triggered by Katakana reading

The covert letter-by-letter reading of Katakana evoked many MEG spikes that fulfilled the ECD criteria (103 times /3890 s) (the number of spikes/task duration in total of 2 sessions), whereas that of Hiragana and Kanji and the task of finding specific strings among the random-aligned marks provoked fewer ones

(Hiragana: 3 times /641 s, Kanji: 5 times /585 s, finding specific strings: 1 time /358 s). In Katakana reading, 91 ECDs out of 103 spike-complex were calculated as a single ECD and clustered in the posterior part of the left basal temporal area (pBTA). The averaged MNI coordinate of 91 ECDs was located at (x, y, z = −44, −46, −26). More spikes were provoked in the second session (73) than in the first session (18).

In 8 out of 91 ECDs, an additional ECD was estimated in the left ventral PrCG/frontal operculum with a little time difference to the one at the left pBTA. All 8 pairs of ECDs were detected during the second Katakana reading session when the patient performed Katakana reading for a total of more than 36 min. ECD at the left ventral PrCG/frontal operculum preceded the one at the left pBTA by 24 ± 7 (mean ± standard deviation) msec (Fig. 2).

3.2. Spike propagation tract

The above results suggested the existence of underlying anatomical white matter pathway between the 2 foci. The left ventral PrCG/frontal operculum and pBTA were traced by probabilistic tractography. The tract ran through the long segment of the arcuate fasciculus (Fig. 3) (Catani et al., 2012; Martino et al., 2013).

3.3. Brain network for Katakana reading

Under the scanner, the performances of the accuracy for each script conditions were 90, 90, and 92% for the Katakana, Kanji, and control conditions, respectively. There was no significant statistical difference among them

[One-way ANOVA, F(2, 47.12) = 0.06, P = 0.94]. Similarly, the mean reaction times did not significantly differ among the conditions of Katakana (0.80 s ± 0.14; mean ± standard deviation), Kanji (0.82 s ± 0.10), and control (0.81 s ± 0.11) [One-way Anova, F(2, 0.21) = 0.06, P = 0.94] in the practice run.

Figure 4A illustrates the representative BOLD signal changes in the left ventral PrCG/frontal operculum (Fig. 4A: Right) and left pBTA (Fig. 4A: Left), respectively. In contrast to control scripts, the Katakana and Kanji words that were meaningful for the patient significantly activated the left pBTA (peak Z values: Katakana = 5.50, Kanji = 7.32) and ventral PrCG/frontal operculum (Katakana = 8.26, Kanji = 5.04) (figure not shown). More importantly, conjunction analysis of Katakana and Kanji words revealed significant activation in the left pBTA (peak Z value = 5.47: Fig. 4A: Left) at around the spike focus induced by Katakana reading. When activation during Katakana and Kanji word reading was compared by subtraction, the left lateral ventral frontal area including the spike focus showed greater activation for Katakana than Kanji (the "Katakana effect", peak Z value = 7.62: Fig. 4A: Right), but this effect was not present in pBTA. On the other hand, no increased activation for Kanji over Katakana was observed in both the regions ("Kanji effect").

4. Discussion

The patient was diagnosed as partial RE because of 1) alexia and stiffness in his cheeks and 2) regional EEG and MEG spikes seen both interictally and during the aura. Absence of the oral myoclonus and generalized or bilateral spikes supports the diagnosis of partial RE. Although ictal EEG patterns were not recorded except for that of aura, clustered ECDs likely indicate that the seizure onset zone or the primary epileptic focus was located in the left posterior basal temporal area. Based on his clinical findings, the symptomatogenic zone is presumed to include both the left ventral frontal area and left posterior basal temporal area.

The aim of this study was to investigate the mechanism of partial RE. Previously, the hyperexcitable zone has been thought to be restricted to the left hemispheric cortical region related to the posterior language area in patients with partial RE. However, this study clearly showed the scientific evidence of network hyperexcitability between the 2 distinct cortices and that linked substructures within the left hemisphere contribute toward the development of epileptic syndromes in a partial RE.

It is currently recognized that the orthographic information is processed in the left pBTA (Brodomann area 37) (Sakurai et al., 2008). In our study, the averaged coordinates of spike ECDs clustered in the left pBTA were situated close to the regions required for the overt Kanji word reading (Sakurai et al., 2000), covert pseudo word reading (Cappa et al., 1998), and the visual word form area (VWFA) (Jobard et al., 2003) (Fig. 4B). Conjunction analysis showed that the reading of Katakana and Kanji words activated the left pBTA overlapping or adjacent to the location of these ECDs (Fig. 4A: Left). These results suggest that the primary epileptogenic area played an important role in word recognition through morphological processing in our patient.

MEG study showed that the patient had an additional epileptogenicity in the left ventral PrCG/frontal operculum. This area was overlapping or adjacent to the activated regions of the Katakana effects in fMRI study (Fig. 4A: Right). Recent functional imaging and lesion studies revealed that left lateral frontal areas, namely, the ventral PrCG and frontal operculum, are involved in articulation processing (Baldo et al., 2011; Price et al., 2003). In addition, the syllabic character of Kana processing is more strongly involved in phonological conversion and articulation as compared with Kanji processing (Thuy et al., 2004). These findings suggested that the significant Katakana effect observed in our patient is predominantly associated with increased demands of phonological conversion and articulation processing during Katakana reading.

Our findings suggested that as proposed in myoclonic RE by previous studies (Ferlazzo et al., 2005), the cerebral networks subserving epileptic activity in partial RE comprise areas of the brain involved in normal articulation and morphological recognition processing.

It was the second session of Katakana letter-by-letter reading (reading more than 30 min) that provoked considerably more spikes in the left pBTA. Moreover, only the second session generated epileptic spikes in the left ventralPrCG/frontal operculum. Although there were only 8 pairs of ECDs localized in the left ventral PrCG/frontal operculum and left pBTA, this interesting observation led us to hypothesize the following mechanism for generation of the clinical epileptic seizure:

1) There is considerable evidence for normal activation in the cortical areas of left pBTA and ventral PrCG/frontal operculum during reading (Taylor et al., 2013). Katakana reading network was very close to or overlapping with seizure onset and symptomatogenic zone.

2) Prolonged Katakana reading provoked epileptic activation in the left pBTA, the presumed primary focus. Given hyperexcitablity in the reading network led to the spike propagation to the left ventral PrCG/frontal operculum via the long segment of the arcuate fasciculi.

3) Reciprocal neuronal excitation or overload of a critical mass of neurons within the left fronto-temporal reading network might have further enhanced normal physiological activation, then epileptic activity and finally provoked seizures.

Depending on the level of the network hyperexcitability, the cumulative effect of more factors may be needed for generation of the paroxysmal response, namely, 1) comprehensive complexity inherent in orthography and 2) letter familiarity. First, the difficulties in reading Katakana can be explained by the feature model of cognitive psychology: strokes can be considered as features that distinguish 1 letter from another. The letter comprising more strokes has more distinctive features. The mean number of strokes in Katakana is less than that in Hiragana and Tibetan, and is almost one-quarter of that in Kanji. Moreover, Katakana has the most angular orthography, whereas Hiragana has the most cursive orthography, and Katakana is prescribed by the position and direction of a stroke (as in ン (n) and ソ (so)). Hence, the Katakana, which comprises fewer distinctive features, needs more effort to be read than both Kanji and Hiragana. This assumption is in agreement with the finding that only Katakana reading with higher degree of cognitive difficulty produced epileptic spikes in the left pBTA during prolonged reading. Second, of the 3 types of written Japanese characters, Katakana letters are less familiar than Kanji and Hiragana, because they are mainly used for words that have been imported from foreign languages.

Our MEG study showed that Katakana reading provoked considerably more spikes in the second session than in the first one, and all 8 pairs of ECDs localized in the left ventral PrCG/frontal operculum and left pBTA were recorded in the second session. These findings suggest that prolonged effort to sustained concentration caused an accumulation effect, which accelerated the excitability in the above spike foci and arcuate fasciculus. This idea supports the hypothesis that, under intrinsic predisposition of network hyper-excitability, the reciprocal neural excitation between the two spike foci contributed to clinical seizures in partial RE.

Spikes in the left ventral PrCG/frontal operculum preceded those in the left pBTA by approximately 24 msec, a reasonable time difference for neural transmission through the arcuate fasciculus according to the study of cortico-cortical evoked potentials (Matsumoto et al., 2004). It is not exactly known why spikes in the ventral PrCG/frontal operculum occurred first. It may be something intrinsic to this patient's frontal-temporal network connectivity, i.e. the higher likelihood of reciprocal neural excitation, that predisposed the patient to transformation of normal physiological activation into epileptic one. Reciprocal neural excitation or, if present, feed-forward and backward loops within this network might account for generation of the preceding spikes in the ventral frontal area.

5. Conclusions

Our results indicate that 1) selective subsystems including articulation and morphological processing served as the seizure onset and symptomatogenic zones and 2) network hyperexcitability within the left hemisphere contributed to the development of clinical seizures in a patient with partial RE. In conclusion, this multimodal case study implicated that, under certain predisposition of network hyper-excitability, prolonged reading could enhance physiological network activity and then epileptic activity, and finally epileptic seizures occurred.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B) 26282218, 26293209, (C) 26330175 from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), and the Research Grants from the Japan Epilepsy Research Foundation.

Conflict of interest

The authors declare no competing financial interests.

References

Amano S, Kondo T. Japanese NTT database series: Lexical properties of Japanese (I). Tokyo: Sanseido, 1999.

Archer JS, Briellmann RS, Syngeniotis A, Abbott DF, Jackson GD. Spike-triggered fMRI in reading epilepsy: Involvement of left frontal cortex working memory area. Neurology 2003;60:415-421.

Baldo JV, Wilkins DP, Ogar J, Willock S, Dronkers NF. Role of the precentral gyrus of the insula in complex articulation. Cortex 2011;47:800-807.

Cappa SF, Perani D, Schnur T, Tettamanti M, Fazio F. The effects of semantic category and knowledge type on lexical-semantic access: A PET study. NeuroImage 1998;8:350-359.

Catani M, Dell'Acqua F, Bizzi A, Forkel SJ, Williams SC, Simmons A, et al. Beyond cortical localization in clinico-anatomical correlation. Cortex 2012;48:1262-1287.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. commission on classification and terminology of the international league against epilepsy. Epilepsia 1989;30:389-399.

Enatsu R, Mikuni N, Usui K, Matsubayashi J, Taki J, Begum T, et al. Hashimoto N. Usefulness of MEG magnetometer for spike detection in patients with mesial temporal epileptic focus. NeuroImage 2008;41:1206-1219.

Engel J,Jr, International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the

ILAE task force on classification and terminology. Epilepsia 2001;42:796-803.

Ferlazzo E, Zifkin BG, Andermann E, Andermann F. Cortical triggers in generalized reflex seizures and epilepsies. Brain 2005;128:700-710.

Jobard G, Crivello F, Tzourio-Mazoyer N. Evaluation of the dual route theory of reading: A metanalysis of 35 neuroimaging studies. NeuroImage 2003;20:693-712.

Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Morita A, et al. Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography. J Neurosurg 2007;106:90-98.

Koutroumanidis M, Koepp MJ, Richardson MP, Camfield C, Agathonikou A, Ried S, et al. The variants of reading epilepsy. A clinical and video-EEG study of 17 patients with reading-induced seizures. Brain 1998;121:1409-1427.

Maillard L, Vignal JP, Raffo E, Vespignani H. Bitemporal form of partial reading epilepsy: Further evidence for an idiopathic localization-related syndrome. Epilepsia 2010;51:165-169.

Martino J, De Witt Hamer PC, Berger MS, Lawton MT, Arnold CM, de Lucas EM, et al. Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: A fiber dissection and DTI tractography study. Brain Struct Funct 2013;218:105-121.

Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: A cortico-cortical evoked potential study. Brain 2004;127:2316-2330.

Matsumoto R, Nair DR, Ikeda A, Fumuro T, Lapresto E, Mikuni N, et al. Parieto-frontal network in humans studied by cortico-cortical evoked potential. Hum Brain Mapp 2012;33:2856-2872.
Oguri T, Sawamoto N, Tabu H, Urayama S, Matsuhashi M, Matsukawa N, et al. Overlapping connections within the motor cortico-basal ganglia circuit: FMRI-tractography analysis. NeuroImage 2013;78:353-362.
Price CJ, Gorno-Tempini ML, Graham KS, Biggio N, Mechelli A, Patterson K, et al. Normal and pathological reading: converging data from lesion and imaging studies. NeuroImage 2003;20 Suppl 1:S30-41.
Radhakrishnan K, Silbert PL, Klass DW. Reading epilepsy. An appraisal of 20 patients diagnosed at the mayo clinic, rochester, minnesota, between 1949 and 1989, and delineation of the epileptic syndrome. Brain 1995;118:75-89.
Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K, Kanazawa I. Different cortical activity in reading of kanji words, kana words and kana nonwords. Brain Res Cogn Brain Res 2000;9:111-115.
Sakurai Y, Terao Y, Ichikawa Y, Ohtsu H, Momose T, Tsuji S, et al. Pure alexia for kana. characterization of alexia with lesions of the inferior occipital cortex. J Neurol Sci 2008;268:48-59.
Salek-Haddadi A, Mayer T, Hamandi K, Symms M, Josephs O, Fluegel D, et al. Imaging seizure activity: A combined EEG/EMG-fMRI study in reading epilepsy. Epilepsia 2009;50:256-264.
Taylor JS, Rastle K, Davis MH. Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. Psychol Bull 2013;139:766-791.

Thuy DH, Matsuo K, Nakamura K, Toma K, Oga T, Nakai T, et al. Implicit and explicit processing of kanji and kana words and non-words studied with fMRI. NeuroImage 2004;23:878-889.

Vaudano AE, Carmichael DW, Salek-Haddadi A, Rampp S, Stefan H, Lemieux L, et al. Networks involved in seizure initiation. A reading epilepsy case studied with EEG-fMRI and MEG. Neurology 2012;79:249-253.

Wolf P. Epileptic seizures and syndromes: With some of their theoretical implications. London: John Libbey, 1994.

Figure legends

Fig. 1

An example of the screen with randomized strings of Katakana letters. The patient was instructed to read every letter covertly and identify meaningful words among the strings. “ビートルズ” is a Katakana word of the famous singer group “Beatles”.

Fig. 2

(A) MEG spikes and their gradiometer contour maps. Two enlarged MEG spikes with a time difference of 23 msec are clearly identifiable. Each gradiometer contour map indicates 1 dipole in the left hemisphere.

(B) Two different ECD foci were estimated from a spike-complex: one in the left ventral PrCG/frontal operculum (upper) and the other in the left inferior temporal area (lower) (shown on T1-weighted sagittal MRI slices). ECD in the left ventral PrCG/frontal operculum preceded that in the left pBTA by 23 msec.

Fig. 3

(A) T1-weighted sagittal slices showing clusters of ECDs located in the left ventral PrCG/frontal operculum (upper) and left pBTA (lower).

(B) Three-dimensional reconstructions of functional information including the 2 ROIs (blue) and the result of probabilistic tractography (red).

The white matter fiber tract that links the 2 ROIs via a dorsal projection arching around the Sylvian fissure is thought to be the long segment of the arcuate fasciculus.

Fig. 4

(A) The mean location of paired spike ECDs (red circles) and brain regions associated with conjunction analysis of Katakana and Kanji > control (blue areas: left column) and Katakana > Kanji (yellow areas: right column) are shown. Left column: Overlap of the two loci suggests that left pBTA plays an important role in word recognition through morphological recognition processing.

Right column: The significant activation observed in left ventral PrCG/frontal operculum may be predominantly associated with increased attention due to the demands of phonological conversion and articulation processing.

(B) MNI coordinates in the present and previous studies.

The mean coordinates of spike ECDs detected in left pBTA in this study (red circle) were situated close to the regions required for pseudoword encoding (blue circle: Cappa et al., 1998), reading Kanji words aloud (yellow circle: Sakurai et al., 2000), and visual word form area (VWFA) (green circle: Jobard et al., 2003), but not for the covert reading of Kana words (white circle: Sakurai et al., 2001).

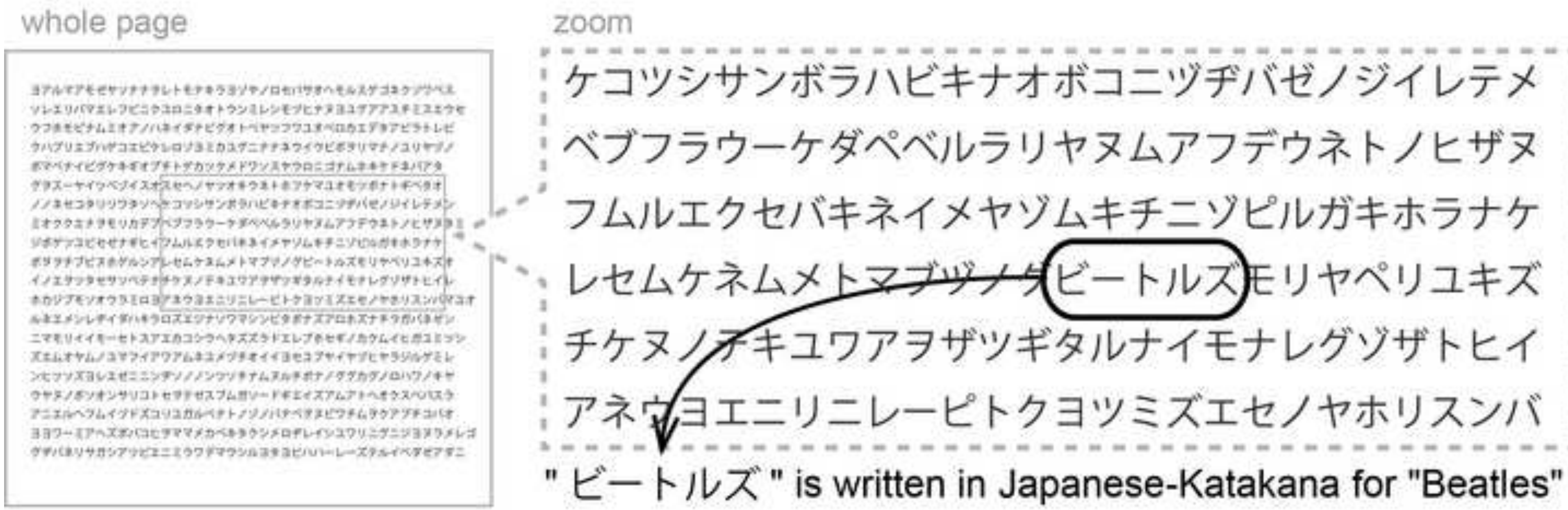
*Cappa et al., 1998

**Sakurai et al., 2000

***Jobard et al., 2003

****Sakurai et al., 2001

Figure 1



" ビートルズ " is written in Japanese-Katakana for "Beatles"

Figure 2

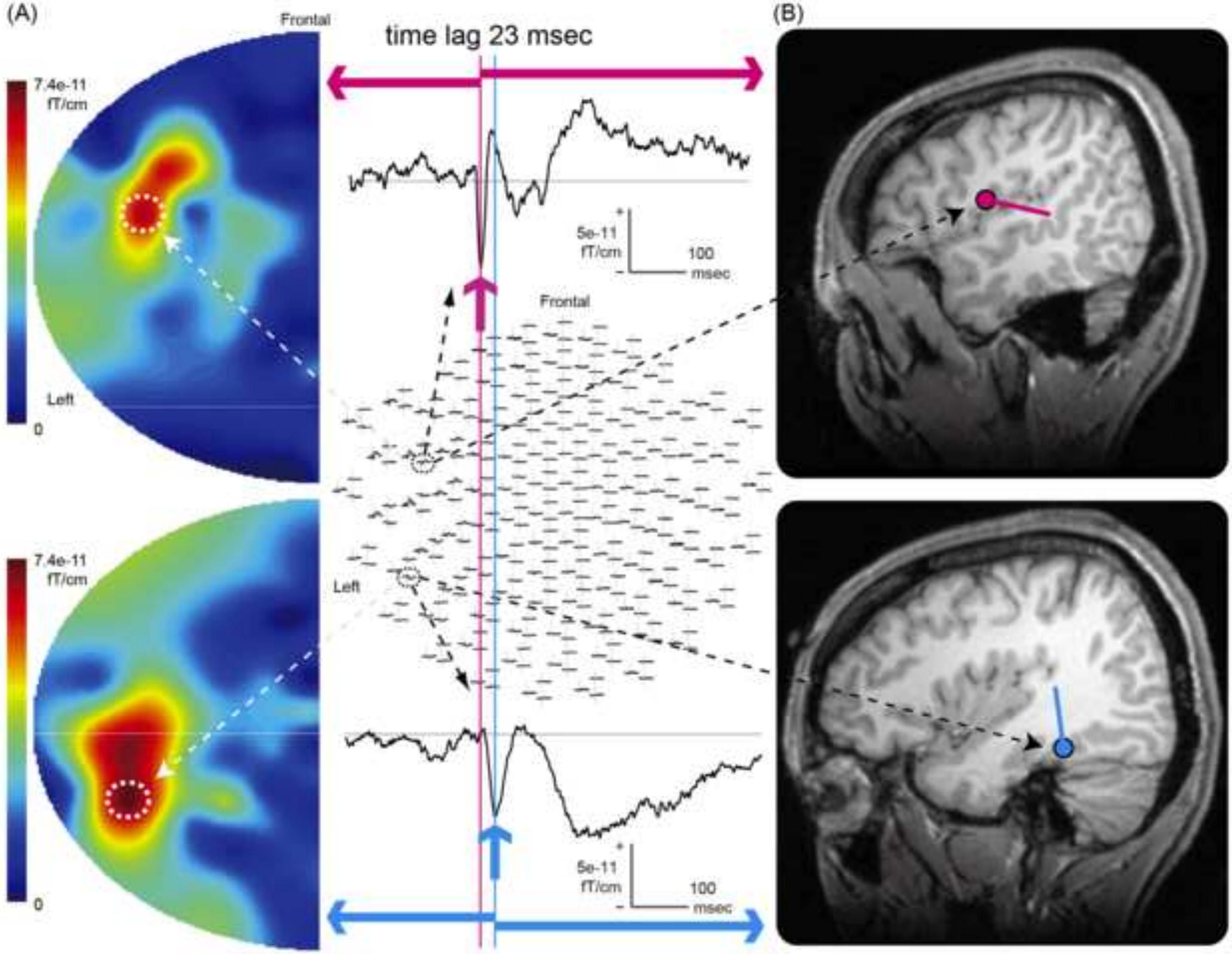

(A)
(B)
Frontal
time lag 23 msec
7.4e-11
fT/cm
Left
0
5e-11
fT/cm
100
msec
Frontal
Left
7.4e-11
fT/cm
0
5e-11
fT/cm
100
msec

Figure 3

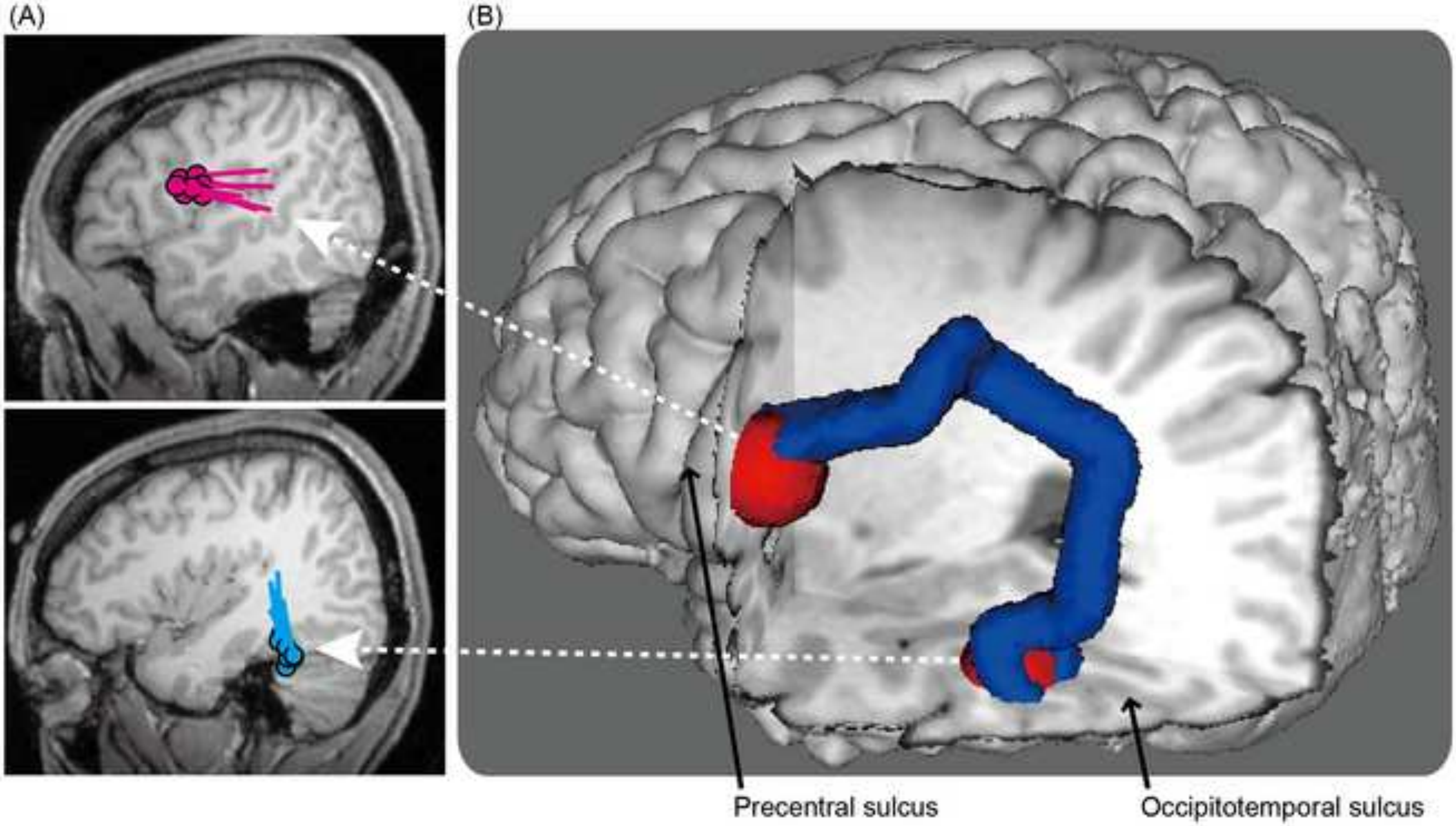
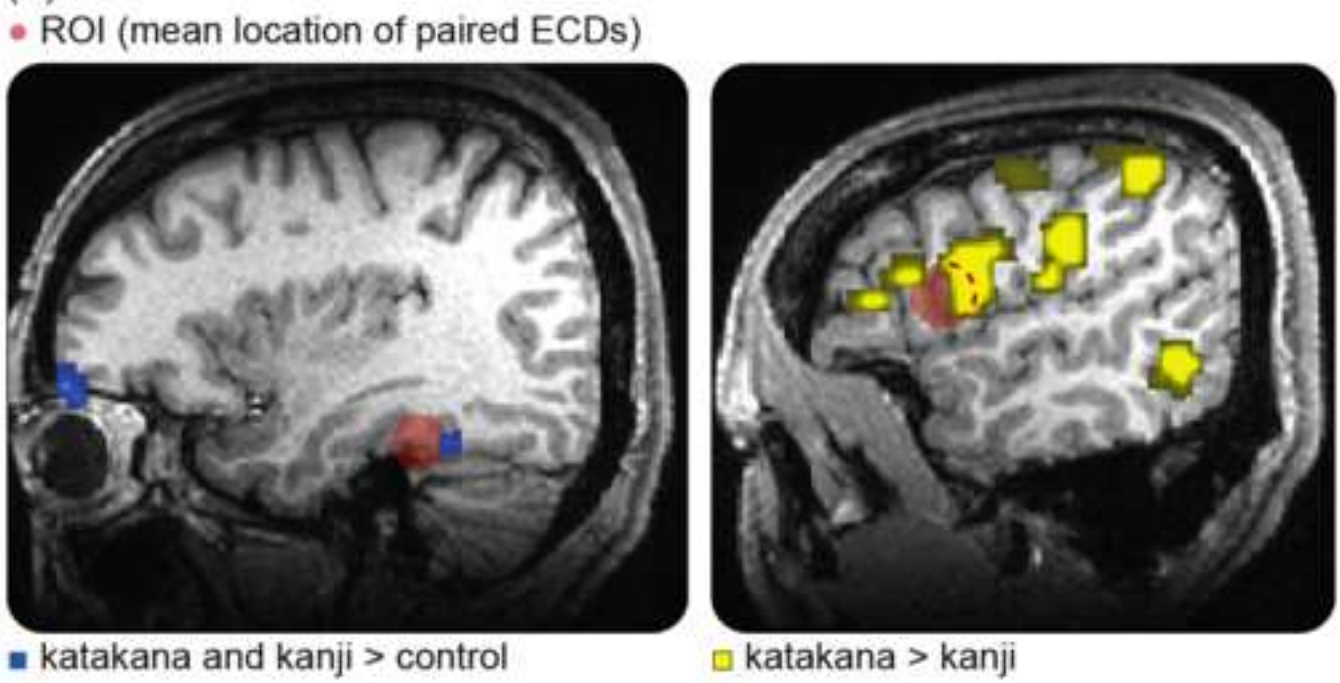


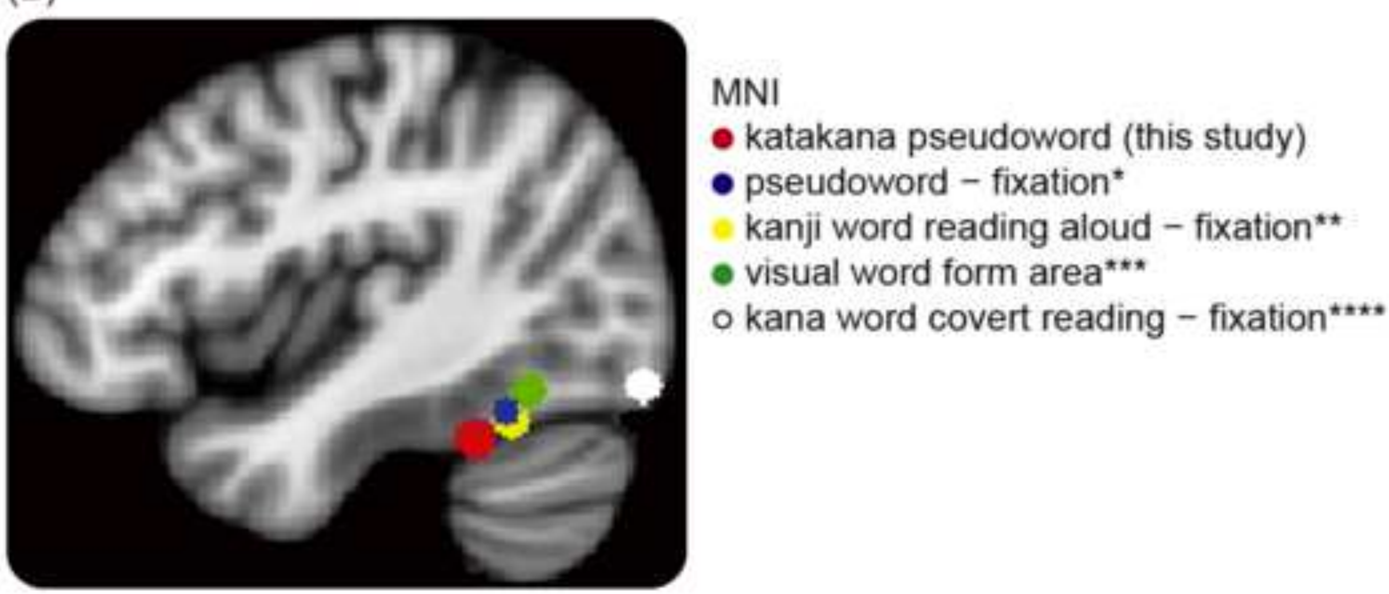
Figure 4

(A)



● ROI (mean location of paired ECDs)
■ katakana and kanji > control
□ katakana > kanji

(B)



MNI
● katakana pseudoword (this study)
● pseudoword − fixation*
● kanji word reading aloud − fixation**
● visual word form area***
○ kana word covert reading − fixation****