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# Characteristic profiles of high gamma activity and blood oxygenation level-dependent responses in various language areas

Naoto Kunii, Kyousuke Kamada *, Takahiro Ota [1], Kensuke Kawai, Nobuhito Saito

*Department of Neurosurgery, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*

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ABSTRACT

High gamma activity (HGA) has been shown to be positively correlated with blood oxygenation level-dependent (BOLD) responses in the primary cortices with simple tasks. It is, however, an open question whether the correlation is simply applied to the association areas related to higher cognitive functions. The aim of this study is to investigate quantitative correlation between HGA and BOLD and their spatial and temporal profiles during semantic processing. Thirteen patients with intractable epilepsy underwent fMRI and electrocorticography (ECoG) with a word interpretation task to evoke language-related responses. Percent signal change of BOLD was calculated at each site of ECoG electrode, which has power amplification of high gamma band (60–120 Hz) activity. We transformed locations of individual electrodes and brains to a universal coordination using SPM8 and made the quantitative comparisons on a template brain. HGAs were increased in several language-related areas such as the inferior frontal and middle temporal gyri and were positively correlated with BOLD responses. The most striking finding was different temporal dynamics of HGAs in the different brain regions. Whereas the frontal lobe showed longer-lasting HGA, the HGA-intensity on the temporal lobe quickly declined. The different temporal dynamics of HGA might explain why routine language-fMRI hardly detected BOLD in the temporal lobe. This study clarified different neural oscillation and BOLD response in various brain regions during semantic processing and will facilitate practical utilization of fMRI for evaluating higher-order cognitive functions not only in basic neuroscience, but also in clinical practice.



## Introduction

A visualization technique of blood oxygenation level-dependent (BOLD) responses was developed as functional magnetic resonance imaging (fMRI) in the 1990s (Ogawa et al., 1990). Since then, fMRI has yielded a wealth of knowledge concerning various brain functions (Price, 2012). Meanwhile, it has been shown that fMRI activation includes a lot of subsidiary cortical areas unnecessary for actual implementation of a specific brain function. In particular, higher-order cognitive functions such as language seem to have wider supplementary areas, as several studies have shown that compared the fMRI results with electrocortical stimulation mapping (Bizzi et al., 2008; Kunii et al., 2011; Rutten et al., 2002). To utilize fMRI reliably in a clinical setting, we need to know in which situations the BOLD signal reflects the reality of neural activity. It is, therefore, of paramount importance to evaluate the concordance and dissociation between BOLD responses and underlying neuronal activity.

Power changes of oscillatory neuronal activities in various frequency ranges have recently received particular attention as physiological correlates of BOLD responses. Among them, the augmentation of high gamma activity (HGA) is assumed to reflect localized cortical processing and has been shown to be correlated with BOLD responses, mainly in the primary cortices such as the visual cortices of animals (Goense and Logothetis, 2008; Logothetis et al., 2001; Niessing et al., 2005) and the primary visual, auditory and motor cortices of humans (Hermes et al., 2011; Nir et al., 2007; Scheeringa et al., 2011). This assumption of HGA as a neural correlate of BOLD, that is, HGA–BOLD coupling, is supported by several basic studies as follows. Pharmacological (Hormuzdi et al., 2001; Traub et al., 2001), computer-simulation (Traub et al., 1997; Wang and Buzsaki, 1996) and electrophysiological studies (Cardin et al., 2009) suggested that HGA should be generated by synchronous post-synaptic potentials of fast-spiking GABAergic interneurons incorporated in a cortical assembly. On the other hand, approximately 74% of the energy budget of the brain was estimated to be devoted to post-synaptic potentials (Attwell and Iadecola, 2002). Taking these findings together, it is rational to assume that HGA could account for a large part of the blood oxygenation change.

* Corresponding author at: Department of Neurosurgery, Asahikawa Medical University, Asahikawa, Japan, 2-1, Midorigaoka-Higashi, Asahikawa, Hokkaido 078-8510, Japan. Fax: +81 166 68 2599.
*E-mail address:* kamady-k@umin.ac.jp (K. Kamada).
[1] Present address: Department of Neurosurgery, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, 2-8-29, Musashidai, Fuchu, Tokyo 183-8524, Japan.

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On the other hand, there are a limited number of studies that investigated HGA–BOLD coupling in the association cortex. Lachaux et al. (2007) showed a close spatial correspondence of the coupling using depth electrodes in frontotemporal regions under semantic paradigms. Ojemann et al. (2009) undertook a detailed estimation of HGA–BOLD coupling in the temporal association cortex and found that HGA is a significant regressor of BOLD. Conner et al. (2011) studied the correlation between various frequency bands and BOLD in various cortices using subdural grids and found positive and negative correlations of BOLD with HGA and beta band oscillation, respectively. Although recent studies have gradually elucidated the relationships between brain oscillations and BOLD, detailed analysis of HGA–BOLD coupling in the human association cortices is needed for further progress of neuroimaging and neuroscience fields.

From previous language-fMRI studies, it is known that the temporal language areas are less activated by the various semantic paradigms than the frontal language areas (Kamada et al., 2007; Kunii et al., 2011; Rutten et al., 2002; Veltman et al., 2000). Kamada et al. revealed that fMRI had a higher sensitivity to the frontal language activity while magnetoencephalography to the temporal language activity. Rutten et al. explained that complex tasks such as sentence reading might activate the receptive language functions in the temporal lobe. Despite practical importance of reproducibility in imaging studies, it remains almost unknown why different imaging modalities and language tasks induce spatially different responses. It is important to clarify the fundamental difference between frontal and temporal language dynamics by analysis of HGA–BOLD coupling.

In this study, we focused on spatial and quantitative relationships of HGA–BOLD coupling in language areas. The results should contribute to providing supportive evidence of the robustness of fMRI. In order to elucidate the fundamental neurophysiology of language networks, regional differences between HGA dynamics and fMRI activation were investigated.

## Materials and methods

### Subjects

This study included 23 patients with intractable epilepsy who had undergone implantation of subdural electrodes for diagnostic purposes at the University of Tokyo Hospital since December 2006. Nine patients were excluded because they had a low intelligence quotient (<70) or no chance of preoperative fMRI evaluation. All the patients underwent the Wada test to investigate language lateralization. One patient, who had bilateral language representation as determined by the Wada test, was excluded from further studies. As a result, we investigated 13 patients (5 men, 8 women) with left language dominance. Detailed demographic data are shown in Table 1.

**Table 1**
Patient demographic and clinical characteristics.

| Patient no. | Age (years), sex | Etiology | VIQ | Epileptic focus |
|---|---|---|---|---|
| 1 | 36, Male | Cortical dysplasia | 82 | Right frontal |
| 2 | 50, Female | Cavernous malformation | 91 | Right temporal |
| 3 | 40, Male | Unknown | 85 | Left temporal |
| 4 | 33, Female | Cortical dysplasia | 94 | Left frontal |
| 5 | 40, Male | Unknown | 93 | Right temporal |
| 6 | 26, Female | Unknown | 87 | Right temporal |
| 7 | 47, Female | Cortical dysplasia | 88 | Right temporal |
| 8 | 24, Male | Cortical dysplasia | 83 | Left temporal |
| 9 | 35, Female | Arachnoid cyst | 107 | Left temporal |
| 10 | 21, Male | Middle fossa encephalocele | 79 | Left temporal |
| 11 | 36, Female | Unknown | 72 | Left temporal |
| 12 | 36, Female | Mesial temporal sclerosis | 97 | Left temporal |
| 13 | 22, Female | Unknown | 79 | Right temporal |

VIQ = verbal intelligence quotient.

This study was approved by the research ethics committee of the faculty of medicine, University of Tokyo (approval number 1797). Written informed consent was obtained from each patient or their family before they participated in the study.

### Language-fMRI data acquisition

In all patients, fMRI was performed more than two months before electrode implantation. MR imaging was performed using a 3-tesla MR scanner with echo planar capabilities and a whole-head receive-only coil (Signa, General Electric, USA). During the experiments, foam cushions were used to immobilize the patient's head. Before the fMRI session, three-dimensional T1-weighted MR images (3D-MRI) of the subject's brain were obtained, which consisted of 136 sequential, 1.4-mm-thick axial slices with a resolution of $256 \times 256$ pixels in an FOV of 240 mm. fMRI was performed with a T2*-weighted echo planar imaging sequence (echo time: 35 ms, repetition time: 4000 ms, flip angle: 90 degrees, slice thickness: 4 mm, slice gap: 1 mm, field of view (FOV): 280 mm, matrix: $64 \times 64$, number of slices: 22). Owing to the different head sizes and positions of each patient, we selected a large FOV that could always contain the entire head, fixing the same center of the FOV on the *x*- and *y*-axes for all sessions. This enabled simple and exact co-registration of the different image sessions.

Each fMRI session consisted of three dummy scan volumes, three activation periods, and 4 baseline (rest) periods. During each period, 5 echo planar imaging volumes were collected, yielding a total of 38 imaging volumes. To obtain language-fMRI data, we used a kind of reading task called the word interpretation task as follows.

### Word interpretation task

Visual stimuli were presented on a liquid crystal display monitor, with a mirror above the head coil allowing the patient to see the stimuli. In the reading periods, words consisting of three Japanese letters were presented in a 2000 ms exposure time with interstimulus intervals of 500 ms. All letter strings were white with a black background. The patients were instructed to read the presented word silently and categorize it into “abstract” or “concrete” based on the nature of the word. During the rest periods, the patients passively viewed random dots of destructured letters that had the same luminance as the stimuli so as to eliminate primary visual responses. All words for the semantic tasks were selected from common Japanese words listed in the electronic dictionary produced by the National Institute for Japanese Language.

### Language-fMRI data analysis

The functional imaging data were preprocessed and analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB (The Mathworks, Inc., Natick, MA). The functional scans were realigned, normalized onto a template brain and spatially smoothed using a Gaussian filter (8 mm kernel). Preprocessed data of each patient were analyzed with the standard general linear model (GLM) approach using boxcar predictors convolved with the canonical hemodynamic response function (Friston et al., 1995). Low-frequency noise was removed with a high-pass filter (128 Hz). A second-level random effects analysis was performed on the contrast images generated for each individual to identify brain regions showing reliable differences between reading and rest periods. A *P* value of 0.005 uncorrected threshold was used to estimate the t-map. The resulting *t*-map was superimposed over a three-dimensional template brain using MRIcroN software (second-level fMRI map) (http://www.sph.sc.edu/comd/rorden/mricron/).

We utilized percent signal change of BOLD (BOLD-SC) to quantify the BOLD responses for each individual. A BOLD-SC is defined as the maximum height of the time course estimated for a task condition,