◆ Human Brain Mapping 32:1580–1591 (2011) ◆

Electrocorticographic Correlates of Cognitive Control in A Stroop Task—Intracranial Recording in Epileptic Patients

Shinichiro Koga,[1,2] Robert Rothermel,[3] Csaba Juhász,[1,4] Tetsuro Nagasawa,[1] Sandeep Sood,[5] and Eishi Asano[1,4]*

[1]*Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan 48201*
[2]*Department of Interdisciplinary Medicine, National Center for Child Health and Development (NCCHD), 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan*
[3]*Department of Psychiatry, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan 48201*
[4]*Department of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan 48201*
[5]*Department of Neurosurgery, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan 48201*

Abstract: The human brain executes cognitive control, such as selection of relevant information in the presence of competing irrelevant information, and cognitive control is essential for us to yield a series of optimal behaviors in our daily life. This study assessed electrocorticographic γ-oscillations elicited by cognitive control in the context of the Stroop color-naming paradigm, with a temporal resolution of 10 msec and spatial resolution of 1 cm. Subjects were instructed to overtly read a color word printed in an incongruent color in the reading task, and to overtly name the ink color of a color word printed in an incongruent color in the Stroop color-naming task. The latter task specifically elicited larger γ-augmentations in the dorsolateral-premotor, dorsolateral-prefrontal and supplementary motor areas with considerable inter-subject spatial variability. Such Stroop color-naming-specific γ-augmentations occurred 500 to 200 msec prior to overt responses. Electrical stimulation of the sites showing Stroop color-naming-specific γ-augmentations resulted in temporary naming impairment more frequently than that of the remaining sites. This study has provided direct evidence that a critical process of cognitive control in the context of Stroop color-naming paradigm consists of recruitment of neurons essential for naming located in variable portions of the dorsolateral premotor and prefrontal areas. *Hum Brain Mapp 32:1580–1591, 2011.* © 2010 Wiley-Liss, Inc.

Key words: cognitive control; executive function; intracranial recording; local field potentials; in-vivo animation of event-related γ-oscillations

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: NIH; Contract grant numbers: NS47550, NS64033; Contract grant sponsor: Japanese Epilepsy Research Foundation; Contract grant sponsor: The Japan-North America Medical Exchange Foundation The Mochida Memorial Foundation for Medical and Pharmaceutical Research.

*Correspondence to: Eishi Asano, Division of Pediatric Neurology, Children's Hospital of Michigan, Wayne State University, 3901 Beaubien St., Detroit, MI 48201, USA. E-mail: eishi@pet.wayne.edu

Received for publication 15 April 2010; Revised 7 June 2010; Accepted 23 June 2010

DOI: 10.1002/hbm.21129

Published online 15 September 2010 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

The human brain executes cognitive control, such as selection of relevant information in the presence of competing irrelevant information, and cognitive control is believed to be essential for us to yield a series of optimal behaviors in our daily life [Alvarez and Emory, 2006; Mansouri et al., 2009]. Common laboratory tasks measuring cognitive control include the Stroop color-naming task [Stroop, 1935], in which a subject is asked to name the ink color of a color word printed in an incongruent color (e.g., to answer "Blue" when a word "Red" printed in blue ink is presented). Neuroimaging studies using functional MRI (fMRI) have consistently shown that the Stroop color-naming task is associated with cortical activation of portions of the frontal lobe including the dorsolateral prefrontal-premotor and the anterior cingulate-supplementary motor areas [Banich et al., 2000; Donohue et al., 2008; Kerns et al., 2004; Leung et al., 2000; Liu et al., 2006; MacDonald et al., 2000; Peterson et al., 1999; Richeson et al., 2003]. It was shown that the left dorsolateral prefrontal cortex was more activated by color naming than by word reading, while the anterior cingulate cortex was more active when responding to incongruent stimuli [MacDonald et al., 2000]. It has been proposed that the site responsible for naming is located in the dorsolateral prefrontal-premotor area and that the conflict monitoring system for cognitive control is located in the medial frontal cortex [Botvinick et al., 2004; Verguts and Notebaert, 2009].

Uncertainty exists regarding the causal relationship between this frontal cortical activation and its function necessary to perform the Stroop color-naming task, partly because loss-of-function studies inconsistently replicated impaired performance in the Stroop color-naming task in patients with dorsolateral prefrontal or anterior cingulate dysfunction [Alexander et al., 2007; Fellows and Farah, 2005; Perret, 1974; Stuss et al., 2001; Turken and Swick, 1999; Vanderhasselt et al., 2006, 2007; Wagner et al., 2006]. By taking a group-averaging approach, the majority of previous fMRI studies demonstrated Stroop-task-specific activations with an excellent spatial resolution, but the topography of activated subregions still varies from study to study [Donohue et al., 2008], and inter-subject variability of activation was rarely taken into account [Chin, 2004]. The temporal dynamics of cortical activation elicited by visual perception, cognitive control and relevant responses have not been demonstrated in an order of milliseconds with good anatomical correlation, while the temporal relationship is useful to judge the causal significance of cortical activations [Fuster, 2001; Sahin et al., 2009].

Intracranial electrocorticography (ECoG) recording in epileptic patients can provide us with rare and unique opportunities to monitor neuronal activities in human cerebral cortex [Canolty et al., 2006; Fisch et al., 2009; Jensen et al., 2007; Sahin et al., 2009]. It has been generally accepted that event-related γ-oscillations can measure cortical activation [Cardin et al., 2009; Crone et al., 2006; Engel et al., 2005; Fries et al., 2007; Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999]; augmentation of γ-oscillations is tightly correlated to increased blood oxygen level dependent on fMRI [Koch et al., 2009; Niessing et al., 2005], increased cerebral glucose metabolism on positron emission tomography [Nishida et al., 2008], and increased firing rate on single unit recording [Manning et al., 2009; Ray et al., 2008]. We expected that intracranially recorded γ-augmentation can localize neural activation driven by cognitive control at high spatial (1 cm) and temporal resolution (10 msec) without sacrificing the information regarding inter-subject variability, and that electrical stimulation via intracranial electrodes can reveal the significance of cortical activation represented by γ-augmentation [Crone et al., 1998; Engel et al., 2005; Fukuda et al., 2008]. ECoG can provide neural measures with a much better signal-to-noise ratio and anatomical specificity, compared to scalp electroencephalography and magnetoencephalography. Furthermore, ECoG studies allow subjects to overtly respond [Brown et al., 2008; Fukuda et al., 2010; Sinai et al., 2005; Towle et al., 2008], whereas a manual response has been used in previous fMRI studies [Turken and Swick, 1999].

In this study using the Stroop color-naming task, we hypothesized that variable portions of the prefrontal-premotor cortices participate in cognitive control by increasing the gain of neurons essential for "naming" between perception of a colored word and a relevant response; this central hypothesis was driven by the previously proposed theory that the prefrontal-premotor cortices implement cognitive control by increasing the gain of selected neurons driving relevant behaviors [Duncan, 2001; Koechlin et al., 2003; Mansouri et al., 2009; Miller and Cohen, 2001; Polk et al., 2008]. Specific questions to be addressed in our study are as follows. Question #1 (Topography): Does the Stroop-color naming task specifically augment the amplitude of γ-oscillations in the frontal areas with inter-subject variability? Question #2 (Temporal relationship): Does such γ-augmentation occur following presentation of visual stimuli but prior to overt responses? Question #3 (Virtual lesion effect): Does electrical stimulation of frontal sites showing γ-augmentation specific to the Stroop-color naming task produce temporary naming impairment?

METHODS

Participants

The inclusion criteria of this study consisted of: (i) age 10 years or above; (ii) patients with focal epilepsy undergoing extraoperative subdural ECoG recording as a part of presurgical evaluation in Children's Hospital of Michigan, Detroit [Asano et al., 2009a]; (iii) completion of two word reading tasks, the Stroop color-naming task, an auditory-naming task [Brown et al., 2008], and a visual-naming task, as described below; (iv) completion of functional brain mapping using electrical stimulation [Brown et al., 2008]; (iv) ECoG was sampled from the Rolandic area

TABLE I. Patient profile

Patient/gender/ age (years)	Handedness	Verbal comprehension index	Language dominance on wada test	Medications prior to ECoG	Seizure onset zones on ECoG	Histology
1/F/10	Rt	106	Bilateral language	OXC, TPM	Lt anterior-medial T and Lt P[a]	Tumor in Lt T
2/F/14	Rt	55	Lt-dominant language	LTG, OXC, TPM	Lt medial T	Hippocampal Sclerosis
3/M/17	Rt	109	N/A	LEV, OXC	Lt medial T	Microdysgenesis and Gliosis in Lt T
4/M/17	Rt	110	N/A	OXC	Lt medial T	Tumor in Lt T
5/F/17	Rt	96	N/A	LTG	Lt medial F	Gliosis in Lt F

F, Female; M, Male; Rt, Right; Lt, Left; N/A, Not applicable; OXC, oxcarbazepine; TPM, topiramate; LTG, lamotrigine; LEV, levetiracetam.

All five patients had a history of focal seizures. The locations of subdural electrodes are shown in Supporting Information Figure S3.

[a]In patient #1, the seizure onset zone driving her habitual seizures was localized in the left medial temporal region, whereas a subclinical seizure arose from the left inferior postcentral gyrus.

[Fukuda et al., 2010], portions of the dorsolateral prefrontal and premotor as well as the occipital-temporal areas (Brodmann area 17, 18, 19, or 37; [Asano et al., 2009b]). The exclusion criteria consisted of: (i) the presence of massive brain malformations (such as large porencephaly, perisylvian polymicrogyria or hemimegalencephaly) which are known to severely confound the anatomical landmarks for the central sulcus or calcarine sulcus, (ii) history of previous epilepsy surgery, and (iii) the presence of epilepsia partialis continua. We studied a consecutive series of five native English-speaking patients with a diagnosis of medically uncontrolled focal seizures (age range: 10–17 years; three females) who satisfied both inclusion and exclusion criteria; all subjects had the presumed seizure focus in the left hemisphere (Table I). This study was not designed to address the role of lateral convexity of the right hemisphere in cognitive control, since ECoG was sampled from the left hemisphere (except for patient #5, in whom portions of the right medial frontal, parietal and occipital cortex was sampled by dual-contact electrodes). The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

Extraoperative Video-ECoG Recording

For extraoperative ECoG recording and subsequent functional cortical mapping, platinum grid electrodes (10 mm intercontact distance, 4 mm diameter; Ad-tech, Racine, WI) were surgically implanted as a part of clinical management of medically uncontrolled focal seizures [Asano et al., 2009a]. All electrode plates were stitched to adjacent plates and/or the edge of dura mater, to avoid movement of subdural electrodes after placement. In addition, intraoperative pictures were taken with a digital camera before dural closure, to confirm the spatial accuracy of electrode display on the three-dimensional brain surface reconstructed from MRI [Asano et al., 2009b; Fukuda et al., 2010]. Subsequently, extraoperative video-ECoG recordings were obtained for 3 to 5 days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (sampling frequency: 1,000 Hz; Nihon Kohden America Inc, Foothill Ranch, CA). All antiepileptic medications were discontinued on the day of subdural electrode placement (i.e., off antiepileptic medications during the Stroop color-naming task described below).

Reading and Color-Naming Tasks

All patients underwent reading and color-naming tasks 1 to 2 days following subdural electrode placement. None of the subjects had a seizure within 2 h prior to tasks. Each subject was awake, unsedated, and comfortably seated on the bed in a dimly lit room. Four-colored words ("Red," "Blue," "Green," and "Pink") were visually presented in a pseudorandom sequence during each task containing 40 trials. In the first task (i.e., "congruent" reading task), each word was printed in a congruent ink color, and all subjects were instructed to overtly read the word (e.g., to answer Red when a word Red printed in red ink was presented). In the second task (i.e., incongruent reading task), each word was printed in an incongruent ink color, and subjects were again instructed to overtly read the word (e.g., to answer Red when a word Red printed in blue ink was presented). In the third task (i.e., Stroop color-naming task), each word was printed in an incongruent ink color, and subjects were instructed to overtly name the ink color (e.g., to answer Blue when a word Red printed in blue ink was presented). Our prediction was that both word-reading tasks as well as the Stroop color-naming task would commonly elicit γ-augmentation involving the occipital area (i.e., visual area) following presentation of visual stimuli and that involving the precentral gyrus (i.e., motor area) during overt responses. Another prediction was that the Stroop-color naming task

would specifically elicit γ-augmentation involving the premotor and prefrontal areas prior to overt responses.

Each word in each trial was written in a different font (Supporting Information Fig. S1). Visual stimuli were presented using a 17-inch Acer AL1714 LCD computer monitor (Acer America, San Jose, CA) placed 60 cm in front of subjects; the monitor cables and power cables were placed at least 60 cm away from the subject as well as the ECoG Recording System [Asano et al., 2009b]. The monitor had a refresh rate of 75 Hz and a luminance of 370 cd/m^2. Stimuli were binocularly presented at the center of the monitor, on the black background, for 5,000 msec with an interstimulus interval randomly ranging from 2,000 to 2,500 msec, using Presentation Software (Neurobehavioral Systems Inc, Albany, CA) [Asano et al., 2009b]. The response time was defined as the period between the onsets of presentation of visual stimulus and overt responses, integrated into the Digital ECoG Recording System via its DC input [Brown et al., 2008; Fukuda et al., 2010].

Patient #2 had an additional color-naming task containing 40 trials (Supporting Information Fig. S2). A colored abstract shape (e.g.: square printed in red) was presented, and she was instructed to overtly name its ink color. Our prediction was that dorsolateral frontal sites showing Stroop-specific γ-augmentation would also show γ-augmentation elicited by naming of the color of abstract shapes.

Auditory and Visual Naming Tasks

The main purpose of this study is to determine the underlying function of cortical sites showing cortical activation elicited by the Stroop-color naming task alone and not by either word reading task. We hypothesized that such cortical sites showing Stroop-specific γ-augmentation should be involved in naming [MacDonald et al., 2000]. To test this hypothesis, all subjects underwent auditory- and visual-naming tasks described below. In the auditory-naming task containing 60 trials [Brown et al., 2008], subjects were instructed to overtly name an object following auditory presentation of a question (e.g., to answer "Bird" for a question: "What flies in the sky?"). In the visual-naming task containing 60 trials, subjects were instructed to overtly name a common object presented in gray scale (such as "dog") following visual presentation, and the remaining paradigm parameters were same as the aforementioned reading and color-naming tasks. Our prediction was that the probability of sites showing Stroop-specific γ-augmentation also exhibiting naming-related γ-augmentation would be significantly greater than that of the remaining premotor-prefrontal sites.

Measurement of ECoG Amplitude Modulations Elicited by Tasks

Task-related ECoG amplitude modulations were evaluated using the trigger point set at the onset of responses; this analytic method was designed to evaluate sequential cortical activation associated with perception of given visual-stimuli and overt responses [Brown et al., 2008; Fukuda et al., 2010] and to determine when and what sites showed cortical activation driven by cognitive control in the context of the Stroop color-naming paradigm. The principal method has been previously validated [Asano et al., 2009b; Brown et al., 2008; Fukuda et al., 2008; Hoechstetter et al., 2004; Nagasawa et al., 2010]; the methodological details are described in the Supporting Information.

The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: (i) the patient provided a correct response within 2,800 msec from the onset of visual presentation; (ii) the duration of overt response was less than 1,000 msec; (iii) a period of silence (as a reference period) lasting 400 msec must be available between 1,800 and 2,200 msec following the onset of responses; (iv) the variability of response time must be within 1,000 msec across trials [Brown et al., 2008]. The exclusion criteria were: ECoG trace was affected by artifacts or electrographic seizures or repetitive spike bursts lasting longer than 3 s [Nagasawa et al., 2010]. Exclusion of ECoG epochs was performed by an investigator (S.K.) while being blinded to the final results of time-frequency analysis or electrical neurostimulation. All cortical sites classified as seizure onset zones as well as those involved by a structural lesion were excluded from our time-frequency analyses, in order to minimize the potential effects of epileptogenic lesion [Bragin et al., 1995] on the results of event-related γ-oscillations. All 4,400 msec ECoG epochs (starting 2,200 msec prior to and ending 2,200 msec after the onset of responses) which satisfied all of the inclusion and the exclusion criteria were utilized for the time-frequency ECoG analysis. In short, each suitable ECoG trial was transformed into the time-frequency domain using a complex demodulation technique [Hoechstetter et al., 2004]; the signal in each electrode site was assigned a specific amplitude as a function of frequency and time (relative to the onset of responses). We determined the percentage change in amplitude (averaged across trials) relative to the mean amplitude in a reference period, defined as the resting state of 400 msec in duration between +1,800 and +2,200 msec relative to the onset of responses. To test for statistical significance for each obtained amplitude measure, statistics based on bootstrapping approach was applied to obtain an uncorrected *P*-value at each time-frequency bin, and the Simes-corrected significance level α was set to 0.05 [Simes, 1986]. To reduce the Type I error derived from testing in multiple electrodes, amplitude modulations spanning at least 20 Hz in width and at least 20 msec in duration in a given electrode were declared to be statistically significant [Asano et al., 2009b; Brown et al., 2008; Fukuda et al., 2010; Nagasawa et al., 2010].

Delineation of ECoG Data on Three-Dimensional MRI

ECoG data for each electrode channel were exported to the given electrode site on the individual three-

dimensional brain surface in two different ways [Asano et al., 2009b; Brown et al., 2008; Fukuda et al., 2010; Nagasawa et al., 2010]. Time-frequency plot matrixes created as described above were placed onto a three-dimensional MRI at the cortical sites corresponding to their respective subdural electrode positions (Figs. 1–5). In addition, percentage changes in γ-range amplitudes at 80–100 Hz were sequentially delineated on the individual three-dimensional MRI, in order to animate "when," "where," and "how many fold" γ-oscillations were increased or decreased (Supporting Information Videos S1). Previous ECoG studies showed that language-related spectral modulations commonly involved this range of γ-oscillations [Brown et al., 2008; Canolty et al., 2007; Dalal et al., 2009; Edwards et al., 2010; Fukuda et al., 2010; Jacobs and Kahana, 2009; Sinai et al., 2005; Tanji et al., 2005; Towle et al., 2008]; thus, percentage changes in γ-range amplitudes at 80–100 Hz are appropriate summary measures to delineate sequential cortical activation elicited by language-related tasks [Crone et al., 2006].

Functional Cortical Mapping Using Electrical Neurostimulation

Functional cortical mapping by electrical neurostimulation was performed during extraoperative ECoG recording, using a previously validated clinical method [Asano et al., 2009b; Brown et al., 2008; Fukuda et al., 2010; Nagasawa et al., 2010]; the details are described in the Supporting Information. We determined whether electrical stimulation of the sites showing Stroop-specific γ-augmentation resulted in temporary naming impairment more frequently than that of the remaining sites (Fisher's exact probability test).

RESULTS

Behavioral Data

The behavioral results demonstrated a Stroop effect; the mean response time was 1,360 msec (standard error of the mean [SE]: 25 msec) in the Stroop color-naming task, which was longer than that measured in the task of reading words printed in a congruent ink color (i.e., congruent reading task) (mean response time: 902 msec; SE: 20 msec; $P < 0.001$ on unpaired t-test), as well as that in the task of reading words printed in an incongruent ink color (i.e., incongruent reading task) (mean response time: 1,202 msec; SE: 27 msec; $P < 0.001$).

Gamma-Modulations Elicited by Reading and Color-Naming Tasks

The results of time-frequency ECoG analysis are summarized in Table II. A total of seven sites in the left dorsolateral premotor (Brodmann area 6), two in the left dorsolateral prefrontal (Brodmann areas 9 and 45) and one in the right medial superior frontal sites (Brodmann area 6) showed significant γ-augmentation elicited by the Stroop color-naming task but not by either word-reading task (Figs. 1–6); there was a considerable inter-subject variability in the locations of sites showing γ-augmentation specifically elicited by the Stroop color-naming task. Such Stroop-specific γ-augmentation occurred between presentation of visual stimuli and overt responses, 500 to 200 msec prior to overt responses.

During both word-reading tasks as well as the Stroop color-naming task, significant γ-augmentation was commonly elicited in the lateral-polar occipital area (Brodmann areas 17 and 18) as well as the inferior occipital-temporal area (Brodmann areas 19 and 37) following presentation of visual stimuli; significant γ-augmentation was also commonly elicited in the precentral gyrus (Brodmann area 4), immediately prior to and during overt responses.

Gamma-Modulations Elicited by a Task of Color-Naming of Abstract Shapes

Did a task of color-naming of abstract shapes without conflicting word information also elicit γ-augmentation in the dorsolateral premotor site? In patient #2, a task of color-naming of abstract shapes also elicited significant γ-augmentation in the dorsolateral premotor site showing Stroop-specific γ-augmentation (Fig. 2). In this patient, the mean response time was 1,242 msec (SE: 49 msec) in the Stroop color-naming task, which was longer than that (mean: 993 msec; SE: 41 msec) measured in the task of color-naming of abstract shapes.

Gamma-Modulations Elicited by Auditory-Naming and Picture-Naming Task

Six of the aforementioned 10 premotor-prefrontal sites showing Stroop-specific γ-augmentation also exhibited significant γ-augmentation elicited by either auditory- or visual-naming task (Fig. 6). Conversely, 18 of the remaining 147 premotor-prefrontal sites exhibited significant γ-augmentation elicited by either auditory- or visual-naming task. The probability of sites showing Stroop-specific γ-augmentation also exhibiting naming-related γ-augmentation was 4.9 times greater than that of the remaining premotor-prefrontal sites (60% vs 12%; $P < 0.001$ on Fisher's exact probability test).

Correlation Between ECoG Measures and Symptoms Elicited by Electrical Stimulation

Nine out of the aforementioned 10 frontal sites showing Stroop-specific γ-augmentation were electrically stimulated as a part of cortical mapping procedures; temporary

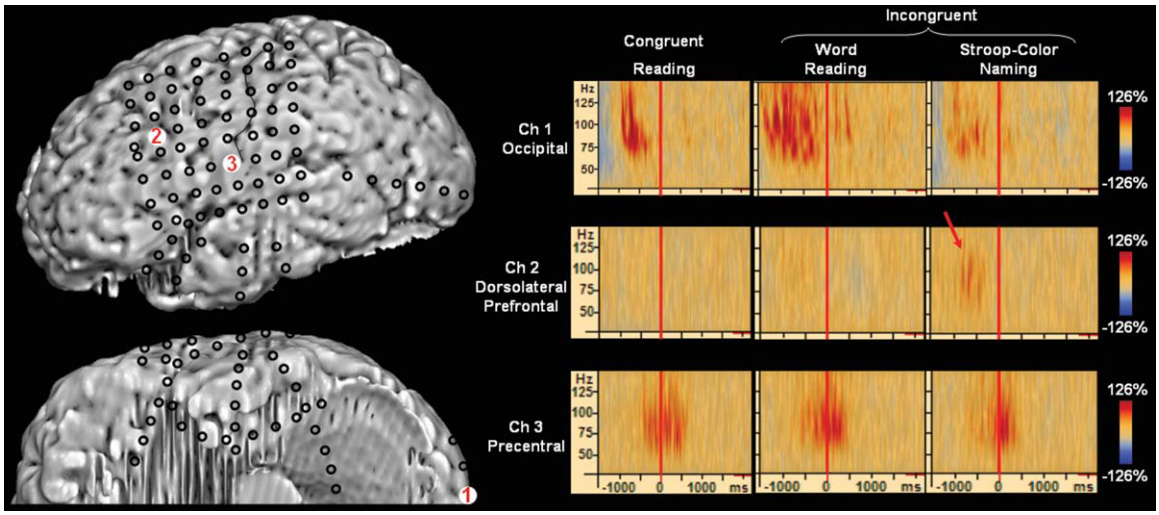

Figure 1.

Event-related γ-modulations in patient #1. Gamma-augmentation commonly elicited regardless of tasks included: Channel 1 in the occipital pole area (Brodmann area 17) and Channel 3 in the precentral gyrus (Brodmann area 4). Significant γ-augmentation specifically elicited by the Stroop color-naming task included: Channel 2 in the dorsolateral prefrontal area denoted by an arrow (Brodmann area 9). Red vertical lines: the onset of overt responses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

naming impairment was elicited by electrical stimulation of four of the nine pairs (44%). All of these four pairs were located in the dorsolateral premotor area. Conversely, electrical stimuli of 21 of the remaining 225 pairs (9.3%) elicited temporary naming impairment. The probability of stimulation of a pair including a site with Stroop-specific γ-augmentation producing temporary naming impairment was 4.8 times greater than that of the remaining pairs ($P = 0.007$ on Fisher's exact probability test).

DISCUSSION

This study has provided direct causal evidence that a critical process of cognitive control in the context of Stroop color-naming paradigm involves recruitment of neurons essential for naming located in variable portions of the dorsolateral premotor and prefrontal areas. The Stroop-color naming task but not word-reading tasks elicited cortical activation represented by γ-augmentation involving the dorsolateral-premotor, dorsolateral-prefrontal and

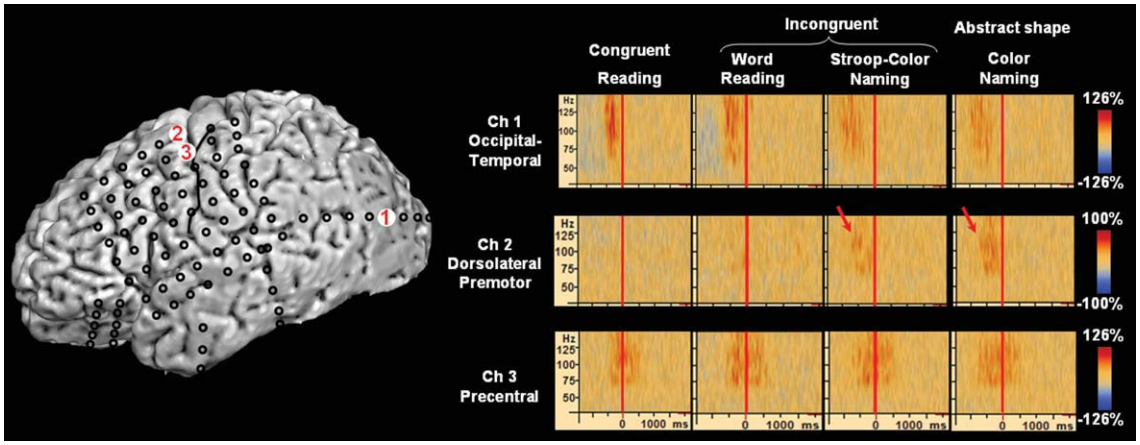

Figure 2.

Event-related γ-modulations in patient #2. Gamma-augmentation commonly elicited by all tasks included: Channel 1 in the occipital-temporal area (Brodmann area 19) and Channel 3 in the precentral gyrus (Brodmann area 4). Significant γ-augmentation was elicited in the dorsolateral premotor area (Brodmann area 6) denoted by arrows by the Stroop color-naming task as well as naming of color of abstract shapes. Red vertical lines: the onset of overt responses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

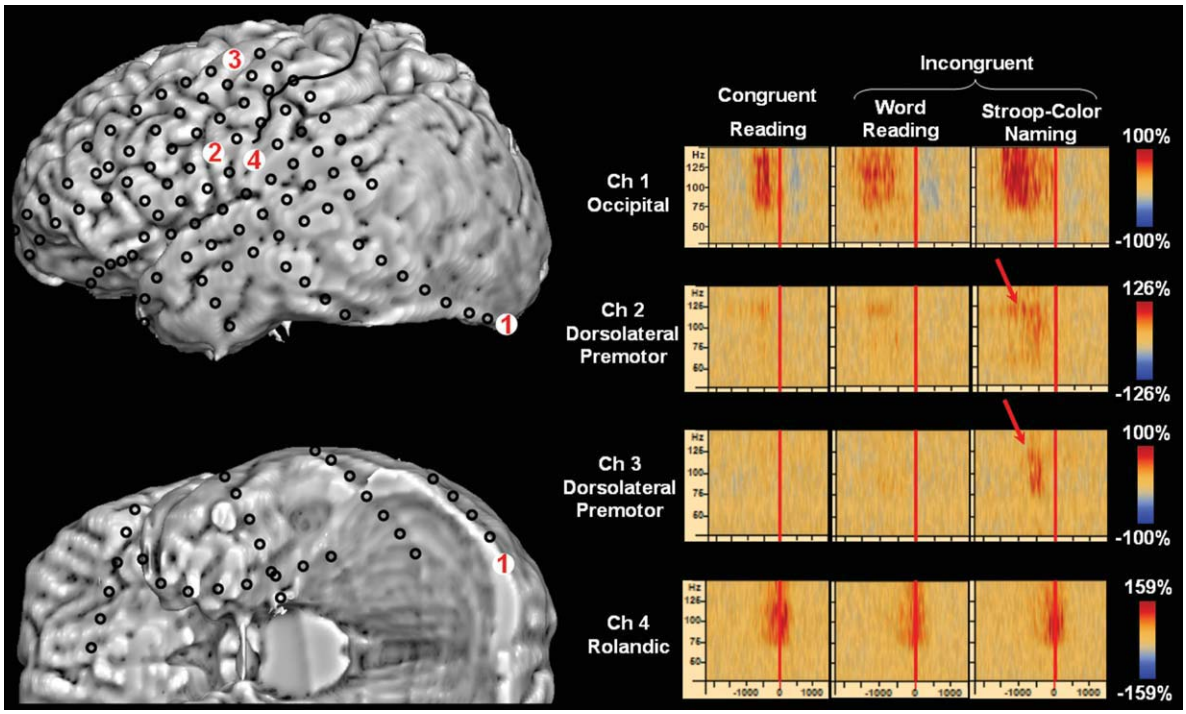

Figure 3.

Event-related γ-modulations in patient #3. Gamma-augmentation commonly elicited regardless of tasks included: Channel 1 in the lateral occipital area (Brodmann area 18) and Channel 4 located in the inferior Rolandic area. Significant γ-augmentation was elicited at Channels 2 and 3 in the dorsolateral premotor areas denoted by arrows (Brodmann area 6) by the Stroop color-naming task. Red vertical lines: the onset of overt responses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

supplementary motor areas with considerable inter-subject variability. Such Stroop-specific γ-augmentation occurred 500 msec to 200 msec prior to overt responses. The frontal sites showing such Stroop-specific γ-augmentation also frequently exhibited γ-augmentation related to other naming tasks. Electrical stimulation of the frontal sites showing such Stroop-specific γ-augmentation produced temporary naming impairment more frequently than that of the remaining sites.

Interpretation of Measures Derived from the Dorsolateral Premotor-Prefrontal Sites

A notable finding in this study is that seven sites showing Stroop-specific γ-augmentation involved the left dorsolateral premotor area (Brodmann area 6), whereas two sites involved the left dorsolateral prefrontal area (Brodmann areas 9 and 45). A total of 53 and 66 electrodes were placed on the dorsolateral premotor and prefrontal areas, respectively (Supporting Information Fig. S3). Thus, the probability of the left dorsolateral premotor area showing Stroop-specific γ-augmentation tended to be greater than that of the left dorsolateral prefrontal area sampled in this study ($P = 0.08$ on two-tail Fisher's exact probability test). This observation is not inconsistent with a previously proposed hypothesis [Koechlin et al., 2003]. It was proposed that cognitive control involves at least three nested levels of processing implemented in distinct frontal subregions, and that the rostral part of the dorsolateral prefrontal area (Brodmann area 46) exerts "episodic controls" affecting the caudal part of dorsolateral prefrontal areas (Brodmann areas 9, 44, and 45), which subsequently exerts "contextual controls" affecting the neighboring premotor area. Finally, according to this hypothesis, the dorsolateral premotor area (Brodmann area 6) exerts "sensory control" involved in selecting motor actions in response to stimuli [Koechlin et al., 2003]. It is plausible that Stroop-specific γ-augmentation seen in the dorsolateral premotor area in this study represented dynamic neural processing at the level of sensory control, although the role of dorsolateral premotor area in inhibiting an automatic behavior (i.e., reading) cannot be completely ruled out. A recent study of healthy adults showed that repetitive transcranial magnetic stimulation (rTMS) at 10 Hz over the dorsolateral premotor area disrupted inhibitory control but not response generation [Muggleton et al., 2010]. It is unlikely that Stroop-specific γ-augmentation in the dorsolateral premotor area simply represented the nonspecific downstream process; Stroop-

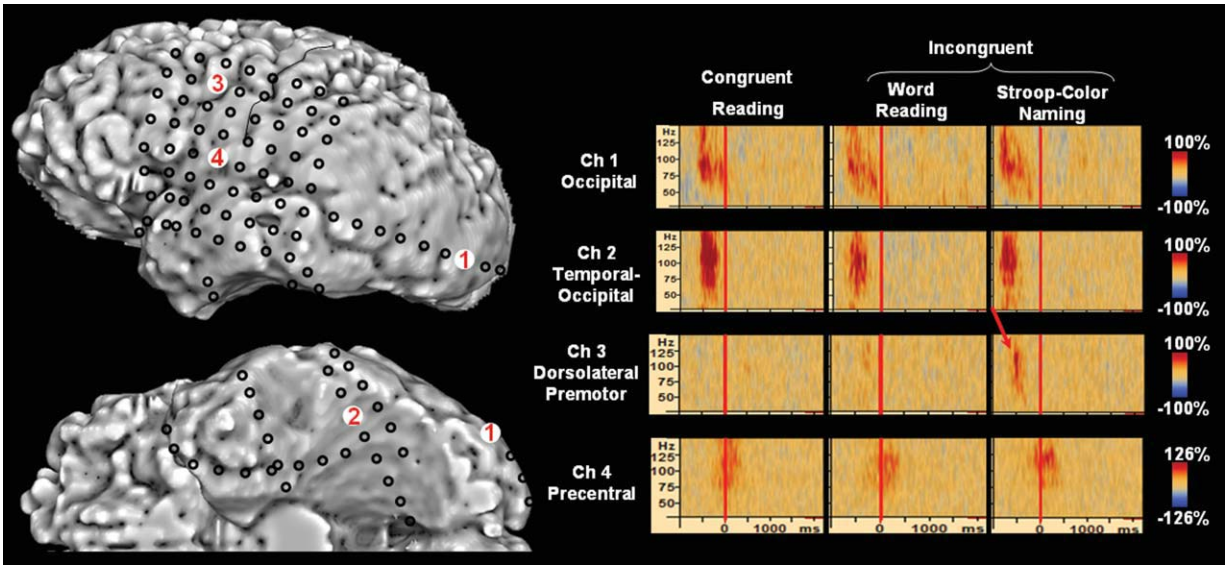

Figure 4.

Event-related γ-modulations in patient #4. Gamma-augmentation commonly elicited by all tasks included: Channel 1 in the lateral occipital area (Brodmann area 18), Channel 2 in the inferior temporal-occipital area (Brodmann area 37) and Channel 4 located in the inferior precentral gyrus. Significant γ-augmentation was elicited at Channel 3 in the dorsolateral premotor area (Brodmann area 6) denoted by an arrow by the Stroop color-naming task. Red vertical lines: the onset of overt responses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

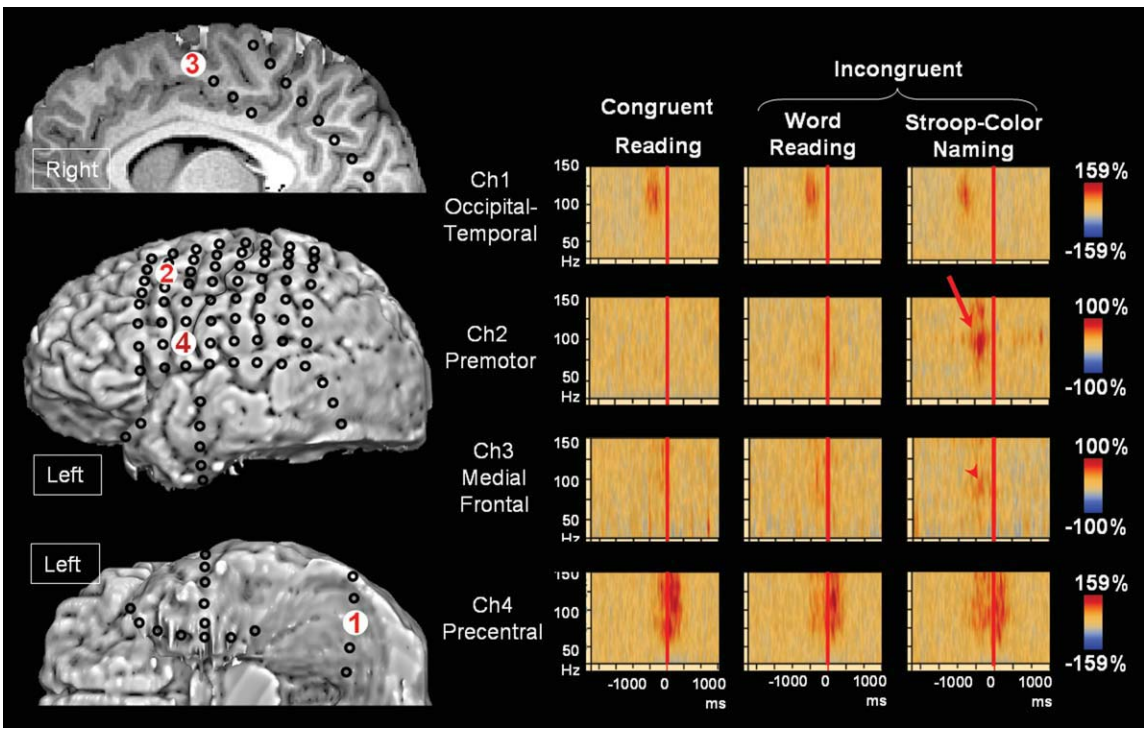

Figure 5.

Event-related γ-modulations in patient #5. Gamma-augmentation commonly elicited by all tasks included: Channel 1 in the occipital-temporal area (Brodmann area 19) and Channel 4 located in the inferior precentral gyrus. Significant γ-augmentation was elicited at Channel 2 in the dorsolateral premotor area (Brodmann area 6) denoted by an arrow by the Stroop color-naming task. Significant γ-augmentation was also elicited at Channel 3 in the right medial frontal area corresponding to the supplementary motor area denoted by an arrowhead. The left supplementary motor area, which was classified as the seizure onset zone, was excluded from time-frequency analysis. Red vertical lines: the onset of overt responses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Gamma-modulations elicited by word reading and Stroop color-naming tasks

	"Congruent" reading task	"Incongruent" reading task	Stroop color-naming task	Frequency range of gamma-augmentation
Lateral-polar occipital area BA 17 and 18	Onset: −590 msec (110 msec) Offset: −180 msec (200 msec)	Onset: −580 msec (440 msec) Offset: −360 msec (230 msec)	Onset: −890 msec (180 msec) Offset: −480 msec (250 msec)	50–150 Hz
Inferior occipital-temporal area BA 19 and 37	Onset: −480 msec (80 msec) Offset: −240 msec (80 msec)	Onset: −560 msec (370 msec) Offset: −350 msec (530 msec)	Onset: −790 msec (130 msec) Offset: −560 msec (160 msec)	50–150 Hz
Dorsolateral prefrontal area BA 9 and 45	NS	NS	Onset: −480 msec (450 msec) Offset: −470 msec (450 msec)	80–100 Hz
Dorsolateral premotor area BA 6	NS	NS	Onset: −530 msec (190 msec) Offset: −320 msec (100 msec)	80–130 Hz
Supplementary motor area BA 6	NS	NS	Onset: −380 msec (NA) Offset: −120 msec (NA)	80–110 Hz
Rolandic area BA 4	Onset: −390 msec (130 msec) Offset: +430 msec (400 msec)	Onset: −380 msec (90 msec) Offset: +380 msec (40 msec)	Onset: −510 msec (240 msec) Offset: +330 msec (370 msec)	50–150 Hz

The median onset and offset of event-related gamma-augmentation relative to overt responses are shown (standard deviation). NS, No significant gamma augmentation was elicited; NA, Not applicable; BA, Brodmann area.

specific γ-augmentation in the dorsolateral premotor area occurred and subsided prior to the onset of overt responses; electrical stimulation of dorsolateral premotor sites showing Stroop-specific γ-augmentation did not elicit sensory-motor symptoms of the mouth or throat but frequently induced temporary naming impairment in this study.

Temporal-spatial ECoG measures available in this study failed to demonstrate that cognitive controls were exerted sequentially by the dorsolateral prefrontal and premotor areas neighboring each other. Previous studies of rTMS have shown variable results. Observations of healthy adults following high-frequency rTMS (at 10–20 Hz) of the left or right dorsolateral prefrontal area failed to notice a significant change in the Stroop interference effect, though rTMS reduced a response time in naming in a nonspecific manner [Vanderhasselt et al., 2006, 2007; Wagner et al., 2006]. Some lesion studies have suggested that large structural lesions involving the left dorsolateral prefrontal-premotor area had a causal association with impaired performance in the Stroop color-naming task [Alexander et al., 2007; Perret, 1974]. One hypothesis is that the dorsolateral prefrontal area might exert cognitive control using its large network with each small subregion contributing to a small extent rather than using a small and intense network. Another hypothesis is that difficulty to find a restricted dorsolateral prefrontal site necessary for cognitive control is due to a considerable inter-subject variability in topography.

In this study, visually driven γ-augmentation in the occipital area and vocalization-driven one in the Rolandic area involved a broad frequency band including 50 to 150 Hz, whereas Stroop-specific γ-augmentation in the frontal areas involved narrower frequency bands commonly including 80 to 100 Hz. We do not know if such a difference can be attributed to the brain topography, the type of tasks or other factors.

Interpretation of ECoG Measures Derived from the Medial Frontal Sites

This study failed to provide strong evidence suggesting that medial frontal areas are necessary for the Stroop color-naming task, due to clinical and sampling limitations. ECoG sampling involved the rostral anterior cingulate cortex on the left side only in one subject (patient #2), who failed to show Stroop-specific γ-augmentation in that area. ECoG sampling bilaterally involved the caudal superior frontal gyrus at the level above the cingulate sulcus in patient #5, whose seizure onset zone involved the left medial frontal area. Only one site in the presumably healthy medial frontal region on the right hemisphere showed Stroop-specific γ-augmentation, but electrical stimulation was not feasible at this site, of which ECoG signals were sampled via the falx; stimulation of this site had a risk of eliciting pain.

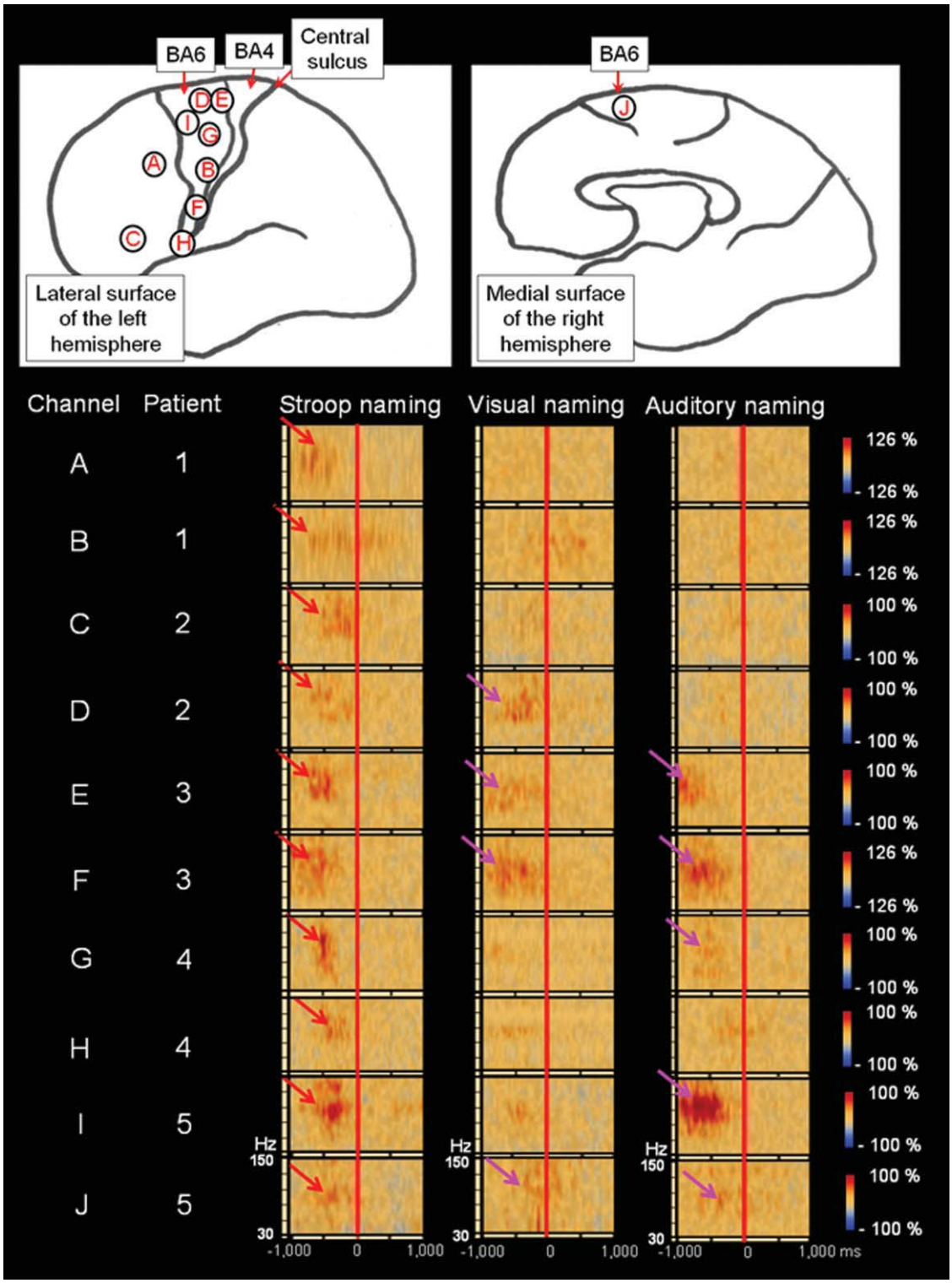

Figure 6.

Naming-related γ-modulations in the sites showing Stroop color-naming-specific γ-augmentation. Left: The results of time-frequency analysis for the Stroop color-naming task. A total of 10 premotor-prefrontal sites showed Stroop-specific γ-augmentation (red arrows). Middle: The results of time-frequency analysis for the visual naming task. Right: The results of time-frequency analysis for the auditory naming task. Six out of the 10 premotor-prefrontal sites showing Stroop-specific γ-augmentation also exhibited significant γ-augmentation elicited by either visual or auditory naming tasks (pink arrows). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

The Stroop-color naming task specifically augmented the amplitude of γ-oscillations in the frontal areas with inter-subject variability. Such γ-augmentation occurred following presentation of visual stimuli but prior to overt responses. Electrical stimulation of frontal sites showing γ-augmentation specific to the Stroop-color naming task produced temporary naming impairment.

ACKNOWLEDGMENTS

The authors are grateful to Harry T. Chugani, MD, Masaaki Nishida, MD, Miho Fukuda, MD, PhD, Hiroki Nariai, MD, Carol Pawlak, REEG/EPT, Ruth Roeder, RN, MS, Alanna Carlson, MA, and the staff of the Division of Electroneurodiagnostics at Children's Hospital of Michigan, Wayne State University, for the collaboration and assistance in performing the studies.

REFERENCES

Alexander MP, Stuss DT, Picton T, Shallice T, Gillingham S (2007): Regional frontal injuries cause distinct impairments in cognitive control. Neurology 68:1515–1523.

Alvarez JA, Emory E (2006): Executive function and the frontal lobes: A meta-analytic review. Neuropsychol Rev 16:17–42.

Asano E, Juhász C, Shah A, Sood S, Chugani HT (2009a) Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery. Brain 132:1038–1047.

Asano E, Nishida M, Fukuda M, Rothermel R, Juhász C, Sood S (2009b) Differential visually-induced gamma-oscillations in human cerebral cortex. Neuroimage 45:477–489.

Banich MT, Milham MP, Atchley R, Cohen NJ, Webb A, Wszalek T, Kramer AF, Liang ZP, Wright A, Shenker J, Magin R (2000): fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. J Cogn Neurosci 12:988–1000.

Botvinick MM, Cohen JD, Carter CS (2004): Conflict monitoring and anterior cingulate cortex: An update. Trends Cogn Sci 8: 539–546.

Bragin A, Jandó G, Nádasdy Z, Hetke J, Wise K, Buzsáki G (1995): Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. J Neurosci 15:47–60.

Brown EC, Rothermel R, Nishida M, Juhász C, Muzik O, Hoechstetter K, Sood S, Chugani HT, Asano E (2008): In vivo animation of auditory-language-induced gamma-oscillations in children with intractable focal epilepsy. Neuroimage 41:1120–1131.

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006): High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626–1628.

Canolty RT, Soltani M, Dalal SS, Edwards E, Dronkers NF, Nagarajan SS, Kirsch HE, Barbaro NM, Knight RT (2007): Spatiotemporal dynamics of word processing in the human brain. Front Neurosci 1:185–196.

Cardin JA, Carlén M, Meletis K, Knoblich U, Zhang F, Deisseroth K, Tsai LH, Moore CI (2009): Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature 459: 663–667.

Chin GJ (2004): Psychology: Individual differences. Science 306:2164–2165.

Crone NE, Miglioretti DL, Gordon B, Lesser RP (1998): Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. Brain 121:2301–2315.

Crone NE, Sinai A, Korzeniewska A (2006): High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res 159:275–295.

Dalal SS, Baillet S, Adam C, Ducorps A, Schwartz D, Jerbi K, Bertrand O, Garnero L, Martinerie J, Lachaux JP (2009): Simultaneous MEG and intracranial EEG recordings during attentive reading. Neuroimage 45:1289–1304.

Donohue SE, Wendelken C, Bunge SA (2008): Neural correlates of preparation for action selection as a function of specific task demands. J Cogn Neurosci 20:694–706.

Duncan J (2001): An adaptive coding model of neural function in prefrontal cortex. Nat Rev Neurosci 2:820–829.

Edwards E, Nagarajan SS, Dalal SS, Canolty RT, Kirsch HE, Barbaro NM, Knight RT (2010): Spatiotemporal imaging of cortical activation during verb generation and picture naming. Neuroimage 50:291–301.

Engel AK, Moll CK, Fried I, Ojemann GA (2005): Invasive recordings from the human brain: Clinical insights and beyond. Nat Rev Neurosci 6:35–47.

Fellows LK, Farah MJ (2005): Is anterior cingulate cortex necessary for cognitive control? Brain 128:788–796.

Fisch L, Privman E, Ramot M, Harel M, Nir Y, Kipervasser S, Andelman F, Neufeld MY, Kramer U, Fried I, Malach R (2009): Neural "ignition": Enhanced activation linked to perceptual awareness in human ventral stream visual cortex. Neuron 64:562–574.

Fries P, Nikolić D, Singer W (2007): The gamma cycle. Trends Neurosci 30:309–316.

Fukuda M, Nishida M, Juhász C, Muzik O, Sood S, Chugani HT, Asano E (2008): Short-latency median-nerve somatosensory-evoked potentials and induced gamma-oscillations in humans. Brain 131:1793–1805.

Fukuda M, Rothermel R, Juhász C, Nishida M, Sood S, Asano E (2010): Cortical gamma-oscillations modulated by listening and overt repetition of phonemes. Neuroimage 49:2735–2745.

Fuster JM (2001): The prefrontal cortex—An update: Time is of the essence. Neuron 30:319–333.

Hoechstetter K, Bornfleth H, Weckesser D, Ille N, Berg P, Scherg M (2004): BESA source coherence: A new method to study cortical oscillatory coupling. Brain Topography 16:233–238.

Jacobs J, Kahana MJ (2009): Neural representations of individual stimuli in humans revealed by gamma-band electrocorticographic activity. J Neurosci 29:10203–10214.

Jensen O, Kaiser J, Lachaux JP (2007): Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 30:317–324.

Kerns JG, Cohen JD, MacDonald AW III, Cho RY, Stenger VA, Carter CS (2004): Anterior cingulate conflict monitoring and adjustments in control. Science 303:1023–1026.

Koch SP, Werner P, Steinbrink J, Fries P, Obrig H (2009): Stimulus-induced and state-dependent sustained gamma activity is tightly coupled to the hemodynamic response in humans. J Neurosci 29:13962–13970.

Koechlin E, Ody C, Kouneiher F (2003): The architecture of cognitive control in the human prefrontal cortex. Science 302:1181–1185.

Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC (2000): An event-related functional MRI study of the stroop color word interference task. Cereb Cortex 10:552–560.

Liu X, Banich MT, Jacobson BL, Tanabe JL (2006): Functional dissociation of attentional selection within PFC: Response and non-response related aspects of attentional selection as ascertained by fMRI. Cereb Cortex 16:827–834.

MacDonald AW III, Cohen JD, Stenger VA, Carter CS (2000): Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288:1835–1838.

Manning JR, Jacobs J, Fried I, Kahana MJ (2009): Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. J Neurosci 29:13613–13620.

Mansouri FA, Tanaka K, Buckley MJ (2009): Conflict-induced behavioural adjustment: A clue to the executive functions of the prefrontal cortex. Nat Rev Neurosci 10:141–152.

Miller EK, Cohen JD (2001): An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202.

Muggleton NG, Chen CY, Tzeng OJL, Hung DL, Juan CH (2010): Inhibitory control and the frontal eye fields. J Cogn Neurosci. Doi: 10.1162/jocn.2010.21416.

Nagasawa T, Rothermel R, Juhász C, Fukuda M, Nishida M, Sood S, Asano E (2010): Cortical gamma-oscillations modulated by auditory-motor tasks: Intracranial recording in patients with epilepsy. Hum Brain Mapp Doi: 10.1002/hbm.20963.

Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RA (2005): Hemodynamic signals correlate tightly with synchronized gamma oscillations. Science 309:948–951.

Nishida M, Juhász C, Sood S, Chugani HT, Asano E (2008): Cortical glucose metabolism positively correlates with gamma-oscillations in nonlesional focal epilepsy. Neuroimage 42:1275–1284.

Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson AW, Gore JC (1999): An fMRI study of Stroop word-color interference: Evidence for cingulate subregions subserving multiple distributed attentional systems. Biol Psychiatry 45:1237–1258.

Perret E (1974): The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. Neuropsychologia 12:323–330.

Pfurtscheller G, Lopes da Silva FH (1999): Event-related EEG/MEG synchronization and desynchronization: Basic principles. Clin Neurophysiol 110:1842–1857.

Polk TA, Drake RM, Jonides JJ, Smith MR, Smith EE (2008): Attention enhances the neural processing of relevant features and suppresses the processing of irrelevant features in humans: A functional magnetic resonance imaging study of the Stroop task. J Neurosci 28:13786–13792.

Ray S, Crone NE, Niebur E, Franaszczuk PJ, Hsiao SS (2008): Neural correlates of high-gamma oscillations (60–200 Hz) in macaque local field potentials and their potential implications in electrocorticography. J Neurosci 28:11526–11536.

Richeson JA, Baird AA, Gordon HL, Heatherton TF, Wyland CL, Trawalter S, Shelton JN (2003): An fMRI investigation of the impact of interracial contact on executive function. Nat Neurosci 6:1323–1328.

Sahin NT, Pinker S, Cash SS, Schomer D, Halgren E (2009): Sequential processing of lexical, grammatical, and phonological information within Broca's area. Science 326:445–449.

Simes RJ (1986): An improved Bonferroni procedure for multiple tests of significance. Biometrika 73:751–754.

Sinai A, Bowers CW, Crainiceanu CM, Boatman D, Gordon B, Lesser RP, Lenz FA, Crone NE (2005): Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. Brain 128:1556–1570.

Stroop JR (1935): Studies of interference in spatial verbal reactions. J Exp Psychol 18:643–662.

Stuss DT, Floden D, Alexander MP, Levine B, Katz D (2001): Stroop performance in focal lesion patients: Dissociation of processes and frontal lobe lesion location. Neuropsychologia 39:771–786.

Tallon-Baudry C, Bertrand O (1999): Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 3:151–162.

Tanji K, Suzuki K, Delorme A, Shamoto H, Nakasato N (2005): High-frequency gamma-band activity in the basal temporal cortex during picture-naming and lexical-decision tasks. J Neurosci 25:3287–3293.

Towle VL, Yoon HA, Castelle M, Edgar JC, Biassou NM, Frim DM, Spire JP, Kohrman MH (2008): ECoG gamma activity during a language task: Differentiating expressive and receptive speech areas. Brain 131:2013–2027.

Turken AU, Swick D (1999): Response selection in the human anterior cingulate cortex. Nat Neurosci 2:920–924.

Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'haenen H (2006): The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. Exp Brain Res 169:279–282.

Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, Clerinx P, D'haenen H (2007): The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. Brain Res 1137:111–116.

Verguts T, Notebaert W (2009): Adaptation by binding: A learning account of cognitive control. Trends Cogn Sci 13:252–257.

Wagner M, Rihs TA, Mosimann UP, Fisch HU, Schlaepfer TE (2006): Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex affects divided attention immediately after cessation of stimulation. J Psychiatr Res 40:315–321.