Published in final edited form as:

Epilepsy Behav. 2012 August ; 24(4): 497–502. doi:10.1016/j.yebeh.2012.05.013.

The Transient Effect of Interictal Spikes from a Frontal Focus on Language-Related Gamma Activity

Erik C Brown^{3,4}, Naoyuki Matsuzaki¹, and Eishi Asano^{1,2,*}

¹Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

²Department of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit Medical Center, Detroit, Michigan, 48201, USA

³MD-PhD Program, School of Medicine, Wayne State University, Detroit, Michigan, 48201, USA

⁴Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, Michigan, 48201, USA

Abstract

Interictal spike activity arising from an epileptic focus may cause transient subclinical changes in language function. We retrospectively studied four patients with a seizure focus of the left frontal lobe who underwent language mapping via electrocorticography. In three patients, we could group language task trials into 'Spike' and 'Non-Spike' trials, based upon occurrence of spikes arising from the seizure onset zone during presentation of question stimuli. In one patient, we demonstrate a reduction in language-related gamma activity (80 – 100Hz) at one dorsal superior frontal site outside the seizure onset zone; reduction in mean peak amplitude of 58.4% of baseline reference (95% C.I.: 31.6% to 85.1%). This site was located near the seizure onset zone and associated with the greatest spike rate among sites of similar function. This is the first preliminary study to show an effect of interictal spikes upon language-related gamma activity of the lateral frontal lobe.

Keywords

Pediatric epilepsy surgery; High-frequency oscillations (HFOs); Event-related synchronization; Naming; Interictal spikes; Inhibition

1. Introduction

The presumption of a deleterious impact of focal epileptic spike-and-wave activity has been held for some time [1]. Indeed, a landmark study by Shewmon and Erwin demonstrated that posteriorly localized spike-and-wave activity was capable of transiently increasing reaction time and error rate in a visual reaction time task [2]. Many studies have also described countless cases of patients exhibiting epileptiform activity in brain regions that appear to correlate with other non-epileptic neuro- or psycho-pathologic phenomena [1–4]. Patients

© 2012 Elsevier Inc. All rights reserved.

*Corresponding Author: Eishi Asano, MD, PhD, MS (CRDSA), Address: Division of Pediatric Neurology, Children's Hospital of Michigan, Wayne State University, 3901 Beaubien St., Detroit, MI, 48201, USA. Phone: 313-745-5547; FAX: 313-745-0955; eishi@pet.wayne.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with interictal spikes involving the left hemisphere are reported to have a greater risk of language-related deficits [5, 6]. Studies combining electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) provide findings that suggest spike-related changes in hemodynamic activity around the seizure focus and beyond [7–10]. The use of a modality with more direct and specific measures to determine the dynamics of transient spike-induced functional deficits is warranted. Since 2007, we have been collecting data regarding the functional modulation of gamma activity (>50Hz) associated with an auditory naming task from patients with focal epilepsy undergoing resection of the presumed epileptic zone following electrocorticography (ECoG) recording [11, 12]. This presents a unique opportunity to explore the direct effect of spontaneous interictal spike activity upon task-based language functions. We aimed to explore the effects of interictal spikes from a well-defined single frontal lobe focus upon higher order language functions. Similar to the method of Shewmon and Erwin, we attempted to group our task trials into ‘Spike’ and ‘Non-Spike’ trials. Our hypothesis upon initiation of the study was that ‘Spike’ trials would be associated with a decrease in subsequent task-related gamma activity in brain regions involved in higher order language function.

2. Methods

We retrospectively searched our patient cohort using the following inclusion criteria: (i) intractable focal epilepsy with an ECoG-defined seizure focus of the left frontal lobe and (ii) mapping of naming-related gamma-augmentation via ECoG using an auditory naming task [11, 12]. In this preliminary study, we selected patients with a frontal lobe focus since our measurements of interest were not early gamma-modulation elicited by acoustic stimuli but those elicited by higher order language function. The following exclusion criteria were applied: (i) multiple seizure foci either within or outside of the frontal lobe, (ii) presence of massive brain malformations (such as large perisylvian polymicrogyria or hemimegalencephaly) which confound anatomical landmarks for the central sulcus and sylvian fissure, or (iii) right language dominance as determined by Wada testing (i.e. intracarotid sodium amobarbital procedure) or left-handedness when Wada test results are not available [13]. We discovered four patient data sets fitting these strict criteria; see Table 1 for details.

All four patients had undergone a period of chronic subdural implantation of electrodes over the left hemisphere, including portions of the frontal lobe anterior to the precentral sulcus, as described previously [11, 12, 14]. The seizure onset zone was visually determined from EEG data, as previously described [15]. An auditory naming task was performed with subsequent evaluation of event-related gamma-augmentations, as previously described in detail [11, 12, 14]. In short, task trials are designed to elicit one- or two-word overt responses; e.g. ‘What flies in the sky?’ In each trial, we measured the response time as defined by the period between stimulus offset and response onset. Time-frequency analysis was performed with a complex demodulation technique implemented in BESA software [16]. We then determined the spatio-temporal dynamics of gamma-augmentations during the task, with bootstrapped statistical tests performed followed by appropriate correction [11, 12]. In this study, we selectively focused on sites that could be classified as Pre-Response based on a previously described categorization scheme [14]; those sites at which peak average gamma-augmentation occurs following stimulus-offset but prior to response-onset, the delay period, as seen in the example provided in Figure 1.

In this study, we grouped trials based on the spontaneous occurrence of interictal spikes during auditory naming task trials. Spikes were detected with the aid of a MatLab-based spike detection algorithm under default settings that have been previously described and validated [17]. This spike detection algorithm was used to aid in the manual detection of

individual spikes as well as to automatically quantify spike counts at individual electrode sites across the time period of the recording during which the language task was performed; about 8 to 14 minutes in duration. Only trials for which a correct answer was provided were included. ‘Spike’ trials were defined with the following criteria: interictal spike(s) originating from the seizure onset zone occurs (i) during the audible question stimulus but (ii) not during the delay period, defined as the time between stimulus-offset and response-onset (Figure 2-A). ‘Non-spike’ trials were defined as those during which no spike originating from the seizure onset zone is detected at any time point between the onset of the audible question stimulus and the onset of the patient’s overt response (Figure 2-B). Spikes occurring at any other time point (e.g. after onset of the patient’s overt response) were disregarded. Due to the spike detection algorithm’s inherent oversensitivity [17], when evaluating for Spike and Non-Spike trials, the authors only removed invalid spike markers (such as sharply contoured deflections due to artifacts), never manually searching for undetected spikes.

For time-frequency analysis of Spike and Non-Spike trials, all trials included were referenced to a common grand-averaged pre-stimulus baseline period. For each electrode site classified as Pre-Response, we determined the peak gamma-augmentation across the frequency range of 80Hz to 100Hz [12] during the delay period for each Spike and Non-Spike trial; we wish to highlight that this time period does not contain interictal spikes in either Spike or Non-Spike trials, as seen in Figure 2. At all sites classified as Pre-Response, we compared the mean peak gamma-augmentation between Spike and Non-Spike trials using a two-sided Independent Samples T-test with no assumption of equal variance, as implemented in IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY, USA). In order to assess more subtle global effects of interictal spikes upon language-related gamma-activity, we compared mean peak gamma-augmentation between Spike and Non-Spike trials at all Pre-Response electrodes across all patients using the Wilcoxon Signed-Ranks test; a non-parametric test of paired samples used when the assumption of a normal distribution is not tenable. All p-values and confidence intervals (C.I.) shown are uncorrected, with 0.05 as the threshold for significance. A Bonferroni correction was employed to account for Type I Error due to multiple comparisons.

3. Results

Spike trials and Non-Spike trials could be identified in three of the four subjects. We failed to identify Spike trials during the task in patient 1, who had sparse interictal spike activity. Only data from patients 2, 3, and 4 were included in subsequent analysis. In patient 2, 16 Spike trials and 13 Non-Spike trials were identified. In patient 3, 4 Spike trials and 8 Non-Spike trials were identified. In patient 4, 10 Spike trials and 65 Non-Spike trials were identified; representative examples of a Spike trial and a Non-Spike trial from patient 4 can be seen in Figure 2. Response times did not differ significantly between Spike and Non-Spike trials, either within or across patients. The grand-average response time was 980ms for Non-Spike trials and 1105ms for Spike trials (p -value = 0.375).

A total of 15 sites were identified as Pre-Response in patient 2; 11 in the frontal lobe, 2 in the parietal lobe, and 2 in the temporal lobe. At no site was a significant difference in peak gamma (80–100Hz) augmentation between Spike and Non-Spike trials discovered. Likewise, no significant difference was observed in patient 3, in whom only a single site of the frontal lobe was identified as Pre-Response. According to the spike-detection algorithm, the interictal spike counts during recording at these sites were much less than that within the seizure onset zone in both of patients 2 and 3; see Table 2 for complete data.

A total of 12 sites were identified as Pre-Response in patient 4; 10 in the lateral frontal lobe and 2 in the medial frontal lobe. Two sites showed a significantly reduced peak gamma augmentation during Spike trials; one site over the precentral gyrus (p -value = 0.01) and one site over the dorsal portion of the superior frontal gyrus (p -value = 0.000078). Only the site over the dorsal portion of the superior frontal gyrus survived Bonferroni correction; reduction in mean peak amplitude was 58.4% of common baseline reference (95% C.I.: 31.6% to 85.1%). Compared to all other 11 Pre-Response sites, this superior frontal site was associated with the largest spike count during the recording, as estimated by the spike-detection algorithm. In fact, the spike count at this electrode was similar to that of the seizure onset zone; see Table 2 for complete data.

Across all electrodes classified as Pre-Response from all patients, we failed to find a significant difference in mean peak gamma augmentation (p -value = 0.219; by Wilcoxon Signed-Ranks Test). See Figure 3 and the Supplementary Figure 1 for electrode-level detail.

4. Discussion

4.1 Primary Finding

The modern era of digital EEG/ECoG processing, long-term recordings, and (semi-) automated spike detection provides the opportunity to search for pathophysiological phenomena associated with interictal spikes on a finer temporo-spatial scale than in the past [18]. We employed these tools in a simple design to retrospectively search our ECoG dataset of auditory language studies for an effect of frontal spikes upon higher order language-related activity. Even in this very limited dataset, at least one electrode site of the frontal lobe in one patient exhibited a reduction in peak gamma activity that cannot simply be attributed to chance. Interictal spikes temporally preceded such a reduction of language-related gamma-activity, and did not contaminate the measurement of gamma-amplitudes during the delay period. This electrode site was physically located near to the seizure onset zone (Figure 3). The same site was also associated with a rate of epileptiform activity that was similar to that of the seizure onset zone, according to a validated, highly sensitive spike detection algorithm [17].

Patients 2 and 3 failed to show any significant spike-related reduction in language-related gamma-activity. In both of these patients we had much lower power to find a difference due to a low number of Spike and Non-Spike trials, relative to patient 4. The Pre-Response sites of both patients 2 and 3 were associated with rates of epileptiform activity that were far lower than their respective seizure onset zones (Table 2). Also, in patient 2, the Pre-Response sites of language-related function were located a physically larger distance away from the seizure onset zone (Supplementary Figure 1); with the seizure onset zone being medial frontal and the Pre-Response sites being either lateral frontal or in another cerebral lobe. It appears that interictal spikes of the seizure onset zone in these two patients did not have a detectable effect upon ongoing language activity.

4.2 Interictal Spikes and Behavior

It has long been postulated that interictal spikes can have a direct influence on normal behavior [1] although the scientific literature provides little information regarding the effects of interictal spikes upon normal electrophysiological dynamics [19]. Shewmon and Erwin were able to demonstrate an increased reaction time, a behavioral measure, related to the chance occurrence of interictal spikes during a visual reaction time task [2, 20]. However, the effect size difference in reported reaction times was on a scale of fractions of a second that would surely go unnoticed in a non-clinical, or even a clinical, setting outside of the confines of a task that demands maximal speed. Indeed, we failed to find a difference in performance between Spike and Non-Spike trials of our auditory language task, which does

not demand maximal speed. The site of patient 4 at which a difference in gamma-augmentation was observed is a cortical region associated with the higher order function of ‘semantic processing’ [21]. Our auditory naming task likely engages semantic processing networks. Thus, it is not surprising that this electrode site of the left superior frontal gyrus was activated and involved in execution of the task. It is also not surprising that task performance was not hindered by spike occurrence when it is considered that most other Pre-Response sites associated with task performance were apparently not affected by spike occurrence and that the difficulty of our auditory naming task is not great, especially for an otherwise near-normal functioning young adult. It may be that interictal spikes occurring during the delay period between question-offset and response-onset may have a more devastating effect on cortical function at Pre-Response sites. However, this is impossible to test with ECoG due to the direct effect of interictal spikes upon electrophysiological measures. In the future, it is warranted to determine whether more frequent or extensive spikes could cause a patient to take a longer time to complete the naming task.

4.3 Conclusion

We have demonstrated that a negative effect of interictal spikes originating from a single frontal lobe focus upon cortical language function: (i) can occur even in the absence of an observable behavioral effect, (ii) may be more prominent at sites nearer to the seizure onset zone, and (iii) may be more prominent at sites associated with epileptiform activity similar to that of the seizure onset zone. It appears that the deleterious effects of interictal spikes are more local and less global in our very small cohort. These results are strictly preliminary and require further validation in a larger cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH grants NS47550 and NS64033 (to E. Asano). We would like to thank Dan Barkmeier, B.S., for helping to clarify the operation of the spike detection algorithm employed in this study. We are grateful to Katsuaki Kojima, M.D., Harry T. Chugani, M.D., Sandeep Sood, M.D., Carol Pawlak, R.EEG./EP.T., Sarah Minarik, R.N., B.S.N., Alanna Marie Carlson, M.A., Elizabeth Bohme, M.A., and the staff of the Division of Electroneurodiagnostics at Children’s Hospital of Michigan, Wayne State University’s School of Medicine, for the collaboration and assistance in performing the studies described above.

References

1. Van Bogaert P, Urbain C, Galer S, Ligot N, Peigneux P, De Tiege X. Impact of focal interictal epileptiform discharges on behaviour and cognition in children. *Neurophysiol Clin.* 2012; 42:53–8. [PubMed: 22200342]
2. Shewmon DA, Erwin RJ. Transient impairment of visual perception induced by single interictal occipital spikes. *J Clin Exp Neuropsychol.* 1989; 11:675–91. [PubMed: 2808657]
3. Volkl-Kernstock S, Bauch-Prater S, Ponocny-Seliger E, Feucht M. Speech and school performance in children with benign partial epilepsy with centro-temporal spikes (BCECTS). *Seizure.* 2009; 18:320–6. [PubMed: 19249229]
4. Massa R, de Saint-Martin A, Carcangiu R, Rudolf G, Seegmuller C, Kleitz C, Metz-Lutz MN, Hirsch E, Marescaux C. EEG criteria predictive of complicated evolution in idiopathic rolandic epilepsy. *Neurology.* 2001; 57:1071–9. [PubMed: 11571336]
5. Binnie CD, Marston D. Cognitive correlates of interictal discharges. *Epilepsia.* 1992; 33 (Suppl 6):S11–7. [PubMed: 1486830]

6. Bedoin N, Ferragne E, Lopez C, Herbillon V, De Bellescize J, des Portes V. Atypical hemispheric asymmetries for the processing of phonological features in children with rolandic epilepsy. *Epilepsy Behav.* 2011; 21:42–51. [PubMed: 21470917]
7. Rathakrishnan R, Moeller F, Levan P, Dubeau F, Gotman J. BOLD signal changes preceding negative responses in EEG-fMRI in patients with focal epilepsy. *Epilepsia.* 2010; 51:1837–45. [PubMed: 20550554]
8. Zijlmans M, Huiskamp G, Hersevoort M, Seppenwoolde JH, van Huffelen AC, Leijten FS. EEG-fMRI in the preoperative work-up for epilepsy surgery. *Brain.* 2007; 130:2343–53. [PubMed: 17586868]
9. Moeller F, Muhle H, Wiegand G, Wolff S, Stephani U, Siniatchkin M. EEG-fMRI study of generalized spike and wave discharges without transitory cognitive impairment. *Epilepsy Behav.* 2010; 18:313–6. [PubMed: 20605747]
10. Jacobs J, Hawco C, Kobayashi E, Boor R, LeVan P, Stephani U, Siniatchkin M, Gotman J. Variability of the hemodynamic response as a function of age and frequency of epileptic discharge in children with epilepsy. *Neuroimage.* 2008; 40:601–14. [PubMed: 18221891]
11. Brown EC, Rothermel R, Nishida M, Juhász C, Muzik O, Hoechstetter K, Sood S, Chugani HT, Asano E. In vivo animation of auditory-language-induced gamma-oscillations in children with intractable focal epilepsy. *Neuroimage.* 2008; 41:1120–31. [PubMed: 18455440]
12. Kojima K, Brown EC, Rothermel R, Carlson A, Matsuzaki N, Shah A, Atkinson M, Mittal S, Fuerst D, Sood S, Asano E. Multimodality language mapping in patients with left-hemispheric language dominance on Wada test. *Clinical Neurophysiology.* 2012 [in press].
13. Knecht S, Drager B, Deppe M, Bobe L, Lohmann H, Floel A, Ringelstein EB, Henningsen H. Handedness and hemispheric language dominance in healthy humans. *Brain.* 2000; 123:2512–8. [PubMed: 11099452]
14. Brown EC, Muzik O, Rothermel R, Matsuzaki N, Juhasz C, Shah AK, Atkinson MD, Fuerst D, Mittal S, Sood S, Diwadkar VA, Asano E. Evaluating reverse speech as a control task with language-related gamma activity on electrocorticography. *Neuroimage.* 2012; 60:2335–45. [PubMed: 22387167]
15. Asano E, Juhasz C, Shah A, Sood S, Chugani HT. Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery. *Brain.* 2009; 132:1038–47. [PubMed: 19286694]
16. Hoechstetter K, Bornfleth H, Weckesser D, Ille N, Berg P, Scherg M. BESA source coherence: a new method to study cortical oscillatory coupling. *Brain Topogr.* 2004; 16:233–8. [PubMed: 15379219]
17. Barkmeier DT, Shah AK, Flanagan D, Atkinson MD, Agarwal R, Fuerst DR, Jafari-Khouzani K, Loeb JA. High inter-reviewer variability of spike detection on intracranial EEG addressed by an automated multi-channel algorithm. *Clin Neurophysiol.* 2011 10.1016/j.clinph.2011.09.023
18. Staley KJ, White A, Dudek FE. Interictal spikes: harbingers or causes of epilepsy? *Neurosci Lett.* 2011; 497:247–50. [PubMed: 21458535]
19. Galanopoulou AS, Moshe SL. The epileptic hypothesis: developmentally related arguments based on animal models. *Epilepsia.* 2009; 50 (Suppl 7):37–42. [PubMed: 19682049]
20. Shewmon DA, Erwin RJ. The effect of focal interictal spikes on perception and reaction time. I. General considerations. *Electroencephalogr Clin Neurophysiol.* 1988; 69:319–37. [PubMed: 2450731]
21. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex.* 2009; 19:2767–96. [PubMed: 19329570]

Figure 1. Example of a 'Pre-Response' Electrode

Data from electrode A30 over the ventral inferior frontal gyrus of patient 4 during performance of the auditory naming task is represented here. The image on the left represents results of analysis when all trials are temporally aligned to the offset of the stimulus questions. The image on the right represents results of analysis when all trials are temporally aligned to the onset of the patient's overt response. As seen, the peak gamma-augmentation during the auditory naming task occurs during the delay period of the task. This type of site is classified as Pre-Response, as previously described [14].

Figure 2. Representative 'Spike' and 'Non-Spike' Trials

Data from patient 4 are presented. (A) displays a Spike trial in which an interictal spike occurs during presentation of the question. No interictal spike occurs during the delay period. (B) displays a Non-Spike trial in which no interictal spike occurs during the trial. Red bars indicate the electrodes over the seizure onset zone of patient 4; electrodes B51, B52, B59, and B60. Channel DC01 represents the audio waveform of the task with subtitles presented beneath. Vertical lines delineate the beginning and end of the delay period during which peak gamma-activity was evaluated. Sites showing significant gamma-augmentation during the delay period between offset of the stimulus and onset of the patient's overt response were defined as Pre-Response sites in the present study.

Figure 3. Pre-Response Electrodes of Patient 4

Data from patient 4 is depicted here. (A) displays the locations of electrodes associated with the seizure onset zone (solid red) and those identified as Pre-Response electrodes (yellow ring) based on evaluation of the gamma activity during an auditory naming task. Electrodes with a yellow ring and a red dot in the center depict Pre-Response electrodes at which gamma activity significantly differed between Spike and Non-Spike trials; solid yellow electrodes were not affected by interictal spikes. Electrodes over inferior and medial brain regions are not shown. (B) shows gamma activity (80Hz to 100Hz) at two sites classified as Pre-Response. In patient 4, 65 Non-Spike and 10 Spike trials were identified; different trials are represented by different color line tracings. Thick horizontal black bars depict the average peak gamma activity during the delay period across trials relative to a common pre-stimulus reference; thin horizontal black lines depict reference level activity (0%). At electrode A56, a significant difference was found that survived Bonferroni correction. Electrode B42 is a representative Pre-Response electrode that was not significantly influenced by the interictal spikes. Time zero, identified by a thin vertical yellow line, represents the onset of the patient's overt response.

Table 1

Patient Data

Patient	Gender	Age at Surgery (years)	Dominant Hand	Age at Epilepsy Onset	Antiepileptic medications	PSI [†]	VCI [†]	VIQ [†]	Schooling	Wada Test [‡] (Language)	Seizure type	ECoG Electrode placement	Seizure Onset Zone	ECoG contacts (total)	Histology
1	Female	10	Rt	10	LEV	112	85	N/A	Average, Normal 6th Grade	N/A	Focal Sz w/sGTC	Lt FPT	Lt dorso-lateral F	74	Low Grade Tumor
2	Female	17	Rt	0	LTG	99	96	97	Average, Normal 12th Grade	N/A	Complex Focal Sz	Lt FPTO	Lt medial F	102	mild Gliosis
3	Male	17	Rt	6	OXC, LTG	56	78	N/A	Special Education, 10th Grade	Lt	Complex Focal Sz	Lt FPTO	Lt dorsal F	116	Gliosis
4	Male	23	Rt	10	LEV, LAC	N/A	N/A	77	Post Normal Secondary School	Lt	Focal Sz w/sGTC	Lt FPT	Lt lateral F	110	mild Gliosis

Epilepsy Behav. Author manuscript; available in PMC 2013 August 01.

LEV:Levetiracetam. LTG:Lamotrigine. LAC:Lacosamide. OXC:Oxcarbazepine. RT:Right. Lt:Left. Sz:Seizure. sGTC:Secondarily Generalized Tonic-Clonic Sz. F:Frontal. T:Temporal. O:Occipital. P:Parietal.

[†] PSI:Processing Speed Index.

[‡] WCI:Verbal Comprehension Index. VIQ:Verbal Intelligence Quotient. Neuropsychological testing was performed based on clinical necessity. Wada testing (i.e. intracarotid sodium amobarbital procedure) results are provided to identify the language-dominant hemisphere. Due to the nature of an auditory language task, we include the measures VIQ and VCI, when available.

Table 2

Spike Trials vs. Non-Spike Trials at Pre-Response Naming Sites

Patient	Electrode	Average Peak Gamma of Delay		Difference (95% C.I.)	Spike Count [†]	Location
		Non-Spike	Spike			
2	Seizure Onset	N/A	N/A	N/A (N/A)	320 (max)	medial frontal
	B10	210.4%	194.5%	15.9% (-55.8% to 87.6%)	131	posterior IFG
	A56	214.5%	218.6%	-4.1% (-82.9% to 74.6%)	130	superior parietal
	A42	210.2%	213.6%	-3.5% (-60.2% to 53.3%)	99	posterior MFG
	A50	247.1%	240.1%	7.0% (-65.9% to 80.0%)	93	posterior MFG
	B1	185.5%	190.2%	-4.7% (-60.2% to 50.9%)	83	posterior MFG
	A41	209.0%	185.0%	2.4% (-29.8% to 77.7%)	72	posterior MFG
	A49	120.3%	136.5%	-16.1% (-61.0% to 28.7%)	62	posterior MFG
	A33	161.7%	179.7%	-17.9% (-72.2% to 36.4%)	61	posterior MFG
	A58	137.3%	138.9%	-1.5% (-34.9% to 31.8%)	38	posterior MFG
	B2	167.9%	187.2%	-19.3% (-75.0% to 36.4%)	32	posterior MFG
	B47	146.0%	149.3%	-3.2% (-42.9% to 36.4%)	26	posterior MTG
	B11	172.2%	203.6%	-31.4% (-75.6% to 12.8%)	17	inferior PreCG
	B16	168.8%	167.3%	1.5% (-50.8% to 53.8%)	15	inferior parietal
	B25	199.6%	224.6%	-2.5% (-89.1% to 39.2%)	9	posterior IFG
	A26	169.0%	162.5%	6.5% (-36.8% to 49.8%)	2	medial temporal
3	Seizure Onset	N/A	N/A	N/A	197 (max)	SFG & MFG
	B20	260.3%	230.4%	29.9% (-85.1% to 144.8%)	1	posterior MFG
4	Seizure Onset	N/A	N/A	N/A	519 (max)	posterior MFG
	A56	181.2%	122.8%	58.4% (31.6% to 85.1%) **	538	middle dorsal SFG
	B42	129.2%	140.9%	-11.7% (-51.1% to 27.7%)	486	posterior MFG
	B18	150.7%	164.6%	-13.9% (-47.6% to 19.8%)	429	medial frontal
	A8	148.5%	156.4%	-7.9% (-37.3% to 21.5%)	380	posterior IFG
	A40	159.9%	168.4%	-8.5% (-40.5% to 23.5%)	375	anterior MFG
	B43	124.3%	196.5%	-72.3% (-254.4% to 109.8%)	368	posterior MFG
	B17	258.4%	269.8%	-11.4% (-82.7% to 59.8%)	351	medial frontal

Patient	Electrode	Average Peak Gamma of Delay		Difference (95% C.I.)	Spike Count [†]	Location
		Non-Spike	Spike			
	B49	208.9%	164.0%	44.9% (12.4% to 77.5%) *	235	PreCG
	A31	149.3%	166.4%	-1.7% (-54.0% to 19.9%)	226	middle IFG
	B35	141.0%	132.7%	8.3% (-31.7% to 48.4%)	170	posterior IFG
	A30	192.6%	193.6%	-1.0% (-33.9% to 32.0%)	93	ventral IFG
	A57	69.5%	75.7%	-6.2% (-33.1% to 20.7%)	77	frontal pole

MTG: Middle Temporal Gyrus. IFG: Inferior Frontal Gyrus. MFG: Middle Frontal Gyrus. SFG: Superior Frontal Gyrus. PreCG: Pre-Central Gyrus. N/A: Not Applicable. C.I.: Confidence Interval.

[†]The spike count is that of the entire task recording session.

^{*} indicates a significant (<0.05) effect of interictal spikes prior to statistical correction.

^{**} indicates that the significant effect survives Bonferroni correction.