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# Heterogeneity of Preictal Dynamics in Human Epileptic Seizures

**ANUP DAS[1], SYDNEY S. CASH[2], AND TERRENCE J. SEJNOWSKI[3,4], (Life Fellow, IEEE)**

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, Stanford, CA 94305, USA
[2]Massachusetts General Hospital, Boston, MA 02114, USA
[3]Division of Biological Sciences, University of California at San Diego, San Diego, CA 92093, USA
[4]Institute for Neural Computation, University of California at San Diego, San Diego, CA 92093, USA

Corresponding author: Anup Das (a1das@stanford.edu)

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**ABSTRACT** It is generally understood that there is a preictal phase in the development of a seizure and this precictal period is the basis for seizure prediction attempts. The focus of this study is the preictal global spatiotemporal dynamics and its intra-patient variability. We analyzed preictal broadband brain connectivity from human electrocorticography (ECoG) recordings of 185 seizures (which included 116 clinical seizures) collected from 12 patients. ECoG electrodes record from only a part of the cortex, leaving large regions of the brain unobserved. Brain connectivity was therefore estimated using the sparse-plus-latent-regularized precision matrix (SLRPM) method, which calculates connectivity from partial correlations of the conditional statistics of the observed regions given the unobserved latent regions. Brain connectivity was quantified using eigenvector centrality (EC), from which a degree of heterogeneity was calculated for the preictal periods of all seizures in each patient. Results from the SLRPM method are compared to those from the sparse-regularized precision matrix (SRPM) and correlation methods, which do not account for the unobserved inputs when estimating brain connectivity. The degree of heterogeneity estimated by the SLRPM method is higher than those estimated by the SRPM and correlation methods for the preictal periods in most patients. These results reveal substantial heterogeneity or desynchronization among brain areas in the preictal period of human epileptic seizures. Furthermore, the SLRPM method identifies more onset channels from the preictal active electrodes compared to the SRPM and correlation methods. Finally, the correlation between the degree of heterogeneity and seizure severity of patients for SLRPM and SRPM methods were lower than that obtained from the correlation method. These results support recent findings suggesting that inhibitory neurons can have anti-seizure effects by inducing variability or heterogeneity across seizures. Understanding how this variability is linked to seizure initiation may lead to better predictions and controlling therapies.

**INDEX TERMS** Connectivity, eigenvector centrality (EC), electrocorticography (ECoG), latent inputs, multivariate Gaussian, partial correlation, sparse-plus-latent-regularized precision matrix (SLRPM).

## I. INTRODUCTION

Epilepsy, characterized by the sudden occurrence of unprovoked seizures, is one of the most common brain disorders, affecting more than 50 million people worldwide. With the goal of being able to predict seizures, many groups have focused on examining signal properties during the preictal period in hopes of finding a biomarker for the impending seizure. While results of these attempts have improved recently [1], we still don't have a practicable seizure prediction system for use in the clinical setting. Part of the difficulty is that we also still don't understand the preictal global spatiotemporal dynamics and its intra-patient variability very well. Recent research [2], [3] in animal models has suggested that neuronal mechanism during the preictal period may also directly influence the degree to which seizures spread and therefore the degree to which they have clinical manifestations [4], [5]. Preictal activity has the potential to predict, to some extent, the likelihood that a seizure would generalize [6]. One outstanding concern in seizure control

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therapy is the stereotypy of the preictal period and one of the challenges in devising a seizure prediction system is the heterogeneity in seizure onset patterns, even in a given patient. Thus, in order to better understand seizure initiation and propagation, it is of paramount importance to study preictal dynamics and its intra-patient variability. Such an understanding could lead to better predictions and controlling therapies [7]–[9].

To analyze the variability of preictal dynamics of seizures within patients, we used a network-based approach [10] and probed brain connectivity from human electrocorticography (ECoG) recordings of 185 seizures (including 116 clinical seizures) collected from 12 patients. Brain connectivity was estimated using the sparse-plus-latent-regularized precision matrix (SLRPM) method. The SLRPM method calculates connectivity from partial correlations of the conditional statistics of the observed regions given the unobserved or latent regions, thus identifying observed regions that are conditionally independent of both the observed and latent regions. Brain connectivity was quantified using the eigenvector centrality (EC) measure, and from this measure, a degree of heterogeneity was calculated for the preictal periods for all seizures in each patient. Results from the SLRPM method are compared to those from the sparse-regularized precision matrix (SRPM) and correlation methods, which do not account for the latent inputs when estimating brain connectivity.

The correlation method is the most widely used method for estimating brain functional connectivity [11]–[14]. Inferring connectivity using the correlation method can be misleading or inaccurate since brain regions might show high correlation due to a common input, which may or may not be measured or observed, and not due to strong physical connections between themselves [15]–[17]. Some researchers have suggested using *partial correlations* to identify direct connections between pairs of brain regions assuming all the regions can be measured [15], [16], [18]–[23]. Partial correlations can find pairwise brain regions which are *conditionally independent* given all the other brain regions thus removing the influence of the common inputs. However, the partial correlation method assumes that all the brain regions are measured or observed, which might lead to incorrect estimation of brain connectivity since most brain regions remain unobserved using current recording technologies, especially in ECoG recordings, which are used in our analysis. The sparse-plus-latent-regularized precision matrix (SLRPM) method is appropriate when there are unobserved or latent regions interacting with the observed regions [24], [25]. The SLRPM method yields partial correlations of the conditional statistics of the observed regions given the latent regions thus identifying observed regions that are conditionally independent of both the observed and latent regions. This method is briefly described in the next section.

## II. METHODS

### A. SLRPM

Assuming that the observed and latent variables jointly follow a multivariate Gaussian distribution, SLRPM solves the following regularized optimization problem (see [25] for a derivation of this optimization problem),

$$\underset{\mathbf{X},\mathbf{L}\, s.t\, \mathbf{X}-\mathbf{L}\succ 0,\, \mathbf{L}\succeq 0}{\arg\min} \big[-\log\det(\mathbf{X}-\mathbf{L}) + \operatorname{tr}(\mathbf{S}(\mathbf{X}-\mathbf{L})) + \alpha\|\mathbf{X}\|_1 + \beta\operatorname{tr}(\mathbf{L})\big], \quad (1)$$

where $\alpha$ and $\beta$ are the regularization parameters balancing the error in the likelihood and the sparse and low rank terms, $\mathbf{S}$ is the sample covariance matrix, $\mathbf{X}$ is the precision matrix of the conditional statistics of the observed variables given the latent variables, and $\mathbf{L}$ is the matrix modeling the effect of the latent inputs. The $L_1$ regularization term $\alpha\|\mathbf{X}\|_1$ imposes sparsity on the underlying brain connectivity and the trace or nuclear norm regularization term $\beta\operatorname{tr}(\mathbf{L})$ imposes low rankness on the common inputs from the latent or unobserved brain regions. Furthermore, these regularizations make the optimization problem well behaved when we have finite number of samples. The optimization problem in (1) is a convex optimization problem and we use the alternating direction method of multipliers (ADMM) [26] to estimate the SLRPM for our analysis.

Application of the SLRPM method on brain connectivity estimation has been limited. In one study [22], the researchers have applied the method to infer connectivity in the mouse visual cortex. SLRPM method outperformed both correlation and SRPM methods in simulations and also found more physiologically interpretable functionally connected brain regions as compared to the correlation and SRPM methods in experimental analysis. In our previous work [25], we have applied the SLRPM method for characterizing preictal and ictal dynamics during epileptic seizures from human ECoG recordings. SLRPM method performed better than the correlation and SRPM methods in simulations and also was applied for seizure detection in 5 patients.

### B. PARTIAL CORRELATION

Assuming that the output (observed variables) of the brain regions follows a multivariate Gaussian distribution, the sparse-regularized precision matrix (SRPM) method was used to calculate partial correlations. SRPM can be estimated by solving the following $L_1$ regularized optimization problem for $\mathbf{X}$

$$\underset{\mathbf{X}\, s.t.\, \mathbf{X}\succ 0}{\arg\min} \big[-\log\det(\mathbf{X}) + \operatorname{tr}(\mathbf{S}\mathbf{X}) + \lambda\|\mathbf{X}\|_1\big], \quad (2)$$

where $\lambda$ is the regularization parameter balancing the error in the maximum likelihood estimate (MLE) of the precision matrix and the sparsity (The MLE of the precision matrix is the inverse of the sample covariance matrix according to the invariance principle) and $\mathbf{S}$ is the sample covariance matrix.

Observe that the optimization problem in (2) is a convex optimization problem and we use the QUIC algorithm [20] to estimate the SRPM for its relatively faster computation time in comparison to others [27], [28].

### C. EIGENVECTOR CENTRALITY (EC)

We quantified brain connectivity using the eigenvector centrality (EC) measure. EC [29] is a measure of the influence or importance of a brain region in the entire brain network. This is based on the concept that a brain region more strongly connected to high influential brain regions will have relatively higher EC. Mathematically, the relative EC $e_i$ of the $i$th brain region can be written as

$$e_i = \frac{1}{\kappa} \sum_j B_{ij} e_j, \tag{3}$$

where $B_{ij}$ is the strength of connectivity (obtained from the connectivity estimation methods (SLRPM/SRPM/correlation)) between brain regions $i$ and $j$ and $e_j$ is the relative EC of the $j$th brain region. In matrix-vector notation, the above set of equations can be compactly written as a eigenvector equation as

$$\mathbf{Be} = \kappa \mathbf{e}, \tag{4}$$

where $\mathbf{B}$ is the estimated connectivity matrix from the methods and $\mathbf{e}$ is its eigenvector. The eigenvector corresponding to the largest positive eigenvalue contains the relative ECs of the brain regions [29] and can be obtained by using the *power method* [25], [29]. We used the brain connectivity toolbox [30] for calculating EC. The EC measure has been previously used by researchers to quantify connectivity in human brain imaging studies [31]–[33] and localize seizure onset zones in epileptic patients [34].

### D. ECoG DATA ACQUISITION AND PROTOCOL

Continuous ECoG recordings from 12 patients (see Supplementary Table 1 for demographics, Supplementary Figures 1-12 for electrode locations) with long-standing pharmaco-resistant complex partial epileptic seizures were analyzed. Recordings were performed using a standard clinical recording system (XLTEK, Natus Medical Inc., San Carlos, CA) with a 500 Hz sampling rate. The reference channel was a strip of electrodes placed outside the dura and facing the skull at a region remote from the other grid and strip electrodes. Subdural electrode arrays were placed to confirm the hypothesized seizure focus and locate epileptogenic tissue in relation to essential cortex, thus directing surgical treatment. The decision to implant, the electrode targets, and the duration of implantation were made entirely on clinical grounds with no input from this research study. All data acquisition was performed under protocols monitored by Institutional Review Board of the Massachusetts General Hospital according to National Institutes of Health guidelines.

### E. PREPROCESSING, REFERENCING, AND ANALYSIS PIPELINE

ECoG recordings were first low pass filtered at 125 Hz using a 6th order Butterworth filter to remove high frequency artifacts. Line frequencies 60 Hz and 120 Hz were then notch filtered using a 4th order Butterworth filter. Next, to reduce the signals from the reference electrode, at each time point, the average signal of all electrodes was subtracted from each electrode [35]–[37] (this process is also known as the common average referencing (CAR)). Finally, recordings were z-scored (mean-variance normalization) for each channel [38].

Methods were applied on 4 s non-overlapping time-windows and brain connectivity was then quantified using EC. A total of 10 minutes before the seizure onset (as determined clinically based on unequivocal ictal activity signatures) was used as the preictal segment. Even though it is difficult to characterize the preictal period of seizures which vary from seizure-to-seizure within a patient and in seizures across patients, we define the 10 minute preseizure period as our preictal period for all seizures in all patients. Such a choice is also similar to those in prior work from other research groups [8], [9], [34], [39].

The regularization parameter $\lambda$ in the SRPM method was set to 0.02 and the regularization parameters $\alpha$ and $\beta$ in the SLRPM method were set to 0.02 and 0.2 respectively for all seizures and all patients. The choice of these regularization parameters was driven in part by simulations using artificial networks [25] and also by the fact that the SRPM and SLRPM methods were found to be robust to changes in the regularization parameters [25] and small changes in the values of these did not significantly change the results and hence, the conclusions of the paper.

## III. RESULTS

### A. HETEROGENEITY EXAMPLE FROM 2 PATIENTS

We consider seizures from 2 patients (patients 1 and 4) as examples and demonstrate that the degree of heterogeneity can be highly variable for seizures across patients. Electrode locations for patients 1 and 4 are shown in Supplementary Figures 1 and 4 respectively. We have analyzed 5 clinical and 2 sub-clinical seizures from patient 1 and 3 clinical seizures from patient 4.

The first important observation is that, in the EC plots of SLRPM method for patient 1 (see Figures 1 (a)-(g), also shown are the 15 minutes post-seizure-onset segments that we have analyzed), the brain regions are uniformly active in the ictal period for the clinical seizures (each of these seizures lasted for approximately 90 seconds) and to some extent, in the sub-clinical seizures, in contrast to the preictal period, where there is relatively more variability across electrodes. Similar conclusions can be drawn for seizures in patient 4, although there is less uniformity in seizure 1 (Figure 4 (a)) than the other two seizures (Figures 4 (b) and (c)) (Also note that the duration of ictal dynamics is relatively large for seizure 1 as compared to those for the other two seizures.).

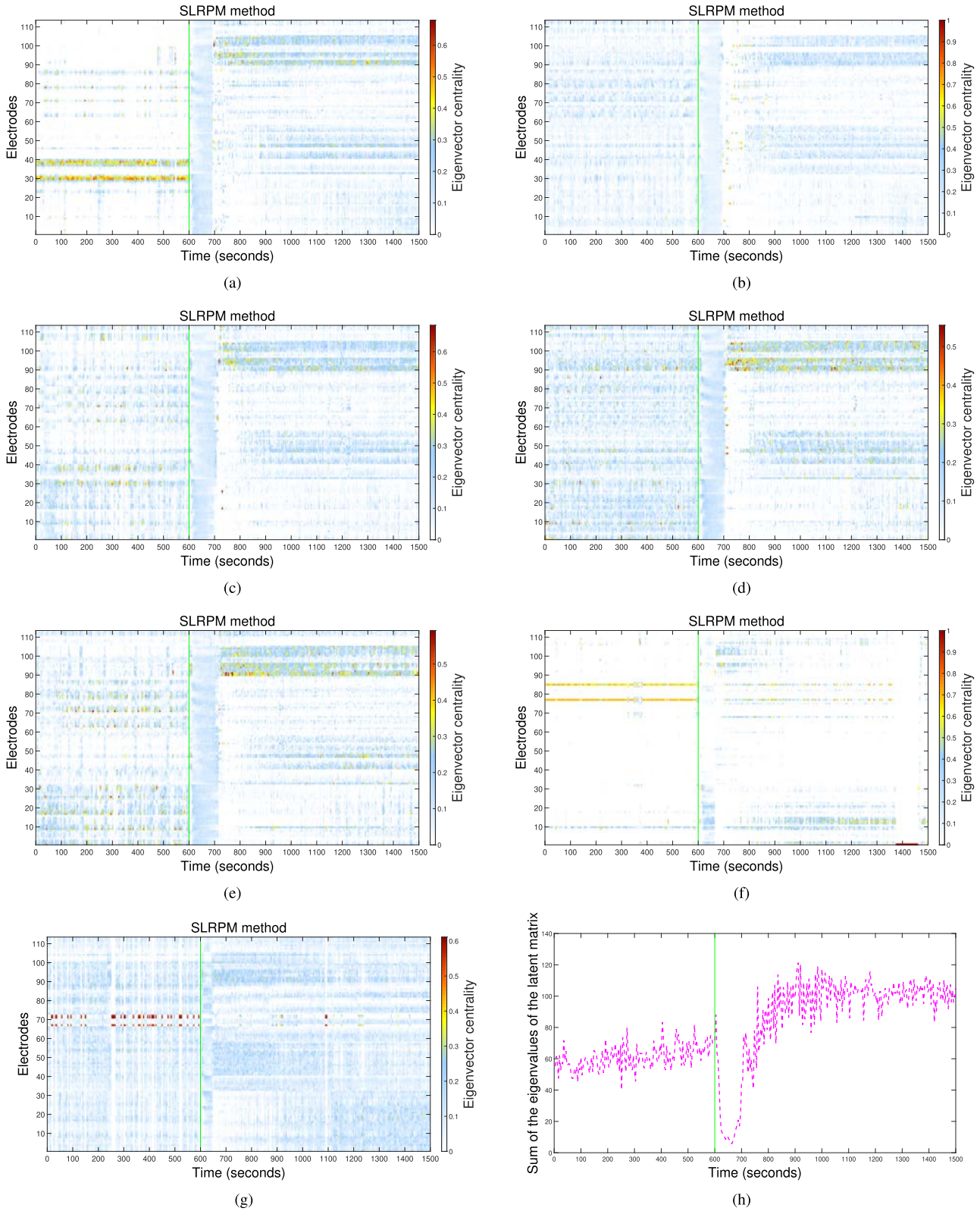


**FIGURE 1.** EC plots for the SLRPM method for clinical ((a)-(e)) and subclinical ((f)-(g)) seizures in patient 1. Also shown is the plot (h) of the latent inputs estimated by the SLRPM method for one example seizure (corresponding to panel (c)) in patient 1. Green lines in all plots denote the seizure onset time.

Uniformity of seizures can also be seen in both patients for the SRPM method (see Figure 2 for patient 1 and Supplementary Figure 13 for patient 4), however no such characteristics can be observed from the EC plots of correlation method

(see Figure 3 for patient 1 and Supplementary Figure 14 for patient 4). Comparison of preictal and ictal dynamics and its implications are discussed in detail in our previous study [25].

The second important observation is that there is high heterogeneity of the preictal active electrodes (by active electrodes, we refer to those electrodes which had relatively high EC across time) across the 7 seizures for the SLRPM method for patient 1. For example, the electrodes which were active in the preictal period of seizure 1 (Figure 1 (a)) did not show up as active electrodes for the preictal period of seizure 2 (Figure 1 (b)). This heterogeneous characteristic was present in the results from the SRPM method, but was absent in the correlation method. Further insights can be inferred by analyzing the latent inputs estimated by the SLRPM method. In order to have a measure for the latent inputs, we calculated the sum of the eigenvalues of the low rank matrix $\mathbf{L}$ estimated by the SLRPM method. An example plot from one clinical seizure (corresponding to Figure 1 (c)) of patient 1 is shown in Figure 1 (h) (also see one example plot of latent inputs (corresponding to Figure 4 (b)) from patient 4 shown in Figure 4 (d) which shows similar characteristics to the plot in Figure 1 (h)). We see that the putative latent inputs are relatively high in the preictal period (and also in the postictal period) in comparison to the ictal period and hence it becomes essential to estimate the precision matrix of the conditional statistics in order to remove the influence of these latent inputs on the recorded activity. The absence of preictal heterogeneity in the correlation results (and to some extent, in the SRPM results) is most probably due to their inability to model the latent inputs and hence these methods might produce erroneous connections among the brain regions, resulting in an erroneous estimate of EC.

In contrast, for patient 4, the preictal active electrodes consistently showed up in all three seizures for the SLRPM method and hence this patient will have a low degree of heterogeneity. Surprisingly, the SRPM method shows relatively high degree of heterogeneity than the SLRPM method and also, both methods have higher heterogeneity than the correlation method (compare Figrues 4 (a)-(c) with Supplementary Figures 13 and 14). Quantification of this degree of heterogeneity for all patients is carried out in the next section.

### B. HETEROGENEITY STATISTICS FOR ALL PATIENTS

In order to calculate the degree of heterogeneity in the preictal period of seizures for a patient, we first calculated the normalized time-average EC in the preictal period of each seizure and then averaged the resulting ECs across all seizures for that patient. We then found the $M$ most active electrodes from the resulting average EC, where $M$ is the number of onset channels marked by the clinician team. We next calculated the coefficient of variability (ratio of standarad deviation to mean) of each active electrode across all seizures for that patient [40]. We define the average coefficient of variability across all active electrodes as the degree of heterogeneity (DH) for the patient. Furthermore, we also reported how many of the active electrodes corresponded to the onset channels marked by the clinician team. We also denote ''A/O'', where ''A'' stands for *active* and ''O'' stands for *onset*, as the ratio of the number of active electrodes corresponding to the onset channels identified by the clinician team to the total number of onset channels identified by the clinical team. We also express the values of DH as percentage. For heterogeneity analysis, we only considered those seizures for which the 10 minutes preictal time-segment did not contain another seizure. The details about the number of seizures analyzed (total 185 seizures out of which 116 were clinical seizures) for each patient for heterogeneity analysis are shown in Supplementary Table 1.

Table 1 shows the heterogeneity statistics for all patients. We observe that DH for SLRPM is higher than that for SRPM for all patients except one (patient 4) and DH for SRPM is higher than that of correlation for all patients. Furthermore we see that the SLRPM method is able to identify relatively more onset channels (28) from the preictal active electrodes in all patients than the SRPM (22) and correlation (21) methods. For SLRPM and SRPM methods, in 5 patients, the preictal active electrodes did not correspond to any of the onset channels whereas for the correlation method, this number increased to 9. Also for SLRPM, only 28 preictal active electrodes corresponded to the onset channels whose total number was 119 in all patients. We also notice that there is no direct relationship between DH and A/O for SLRPM. For example, in patient 4, there is a relatively low DH and none of the active electrodes corresponded to the onset channels. But in patients 2 and 9, for which the seizures have a relatively high DH, 7 and 12 active electrodes corresponded to the onset channels respectively. Furthermore, The DH estimated by SLRPM covered a relatively wider range than those estimated by the SRPM and correlation methods.

We also calculated the correlation between the DH values and seizure severity of the patients for the three methods. Since there were no clinical reports of seizure severity for the patients, the percentage of the channels involved in seizures for the patients were used as a measure of seizure severity. The percentage of channels involved in seizures for each patient was defined to be the total number of onset channels expressed as the percentage of the total number of channels for that particular patient. The correlation values between DH and seizure severity were found to be 0.16, 0.12, and 0.80 for SLRPM, SRPM, and correlation methods respectively.

## IV. DISCUSSION

Even though considerable research has been done to distinguish preictal and ictal dynamics, the variability of seizures within patients is poorly understood. We analyzed brain connectivity from human ECoG recordings of seizures collected from 12 patients. For connectivity analysis, we used the SLRPM method, which estimates connectivity after removing the influence of the latent inputs, which can severely confound the inferred connectivity if not accounted for. Conventional brain connectivity estimation methods such as correlation or Granger causality [41], [42] do not explicitly

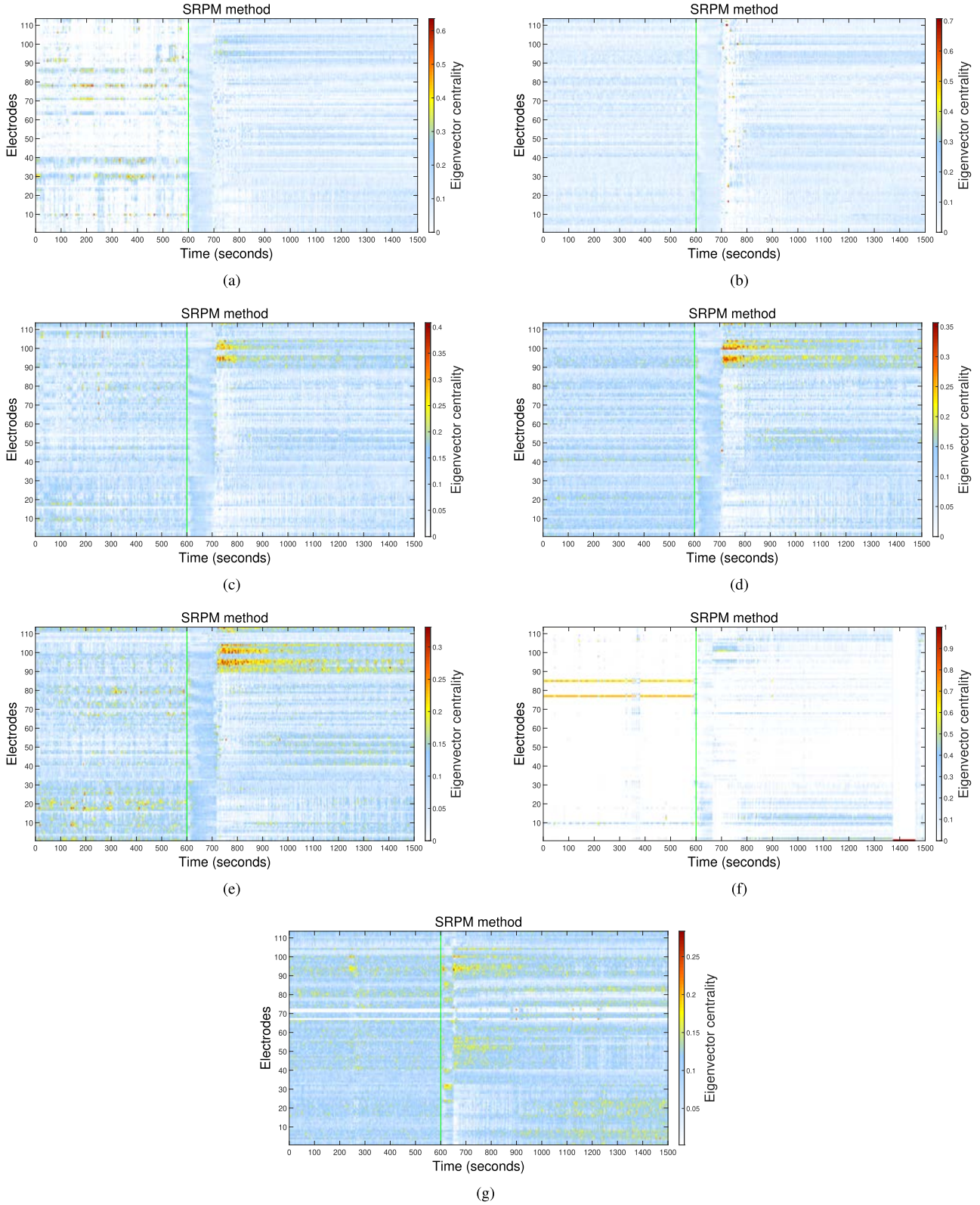


**FIGURE 2.** EC plots for the SRPM method for clinical ((a)-(e)) and subclinical ((f)-(g)) seizures in patient 1. Green lines in all plots denote the seizure onset time.

model the latent inputs and hence can estimate spurious connectivity between brain regions without having any direct connections. Brain connectivity was then quantified using the eigenvector centrality (EC) measure and the degree of

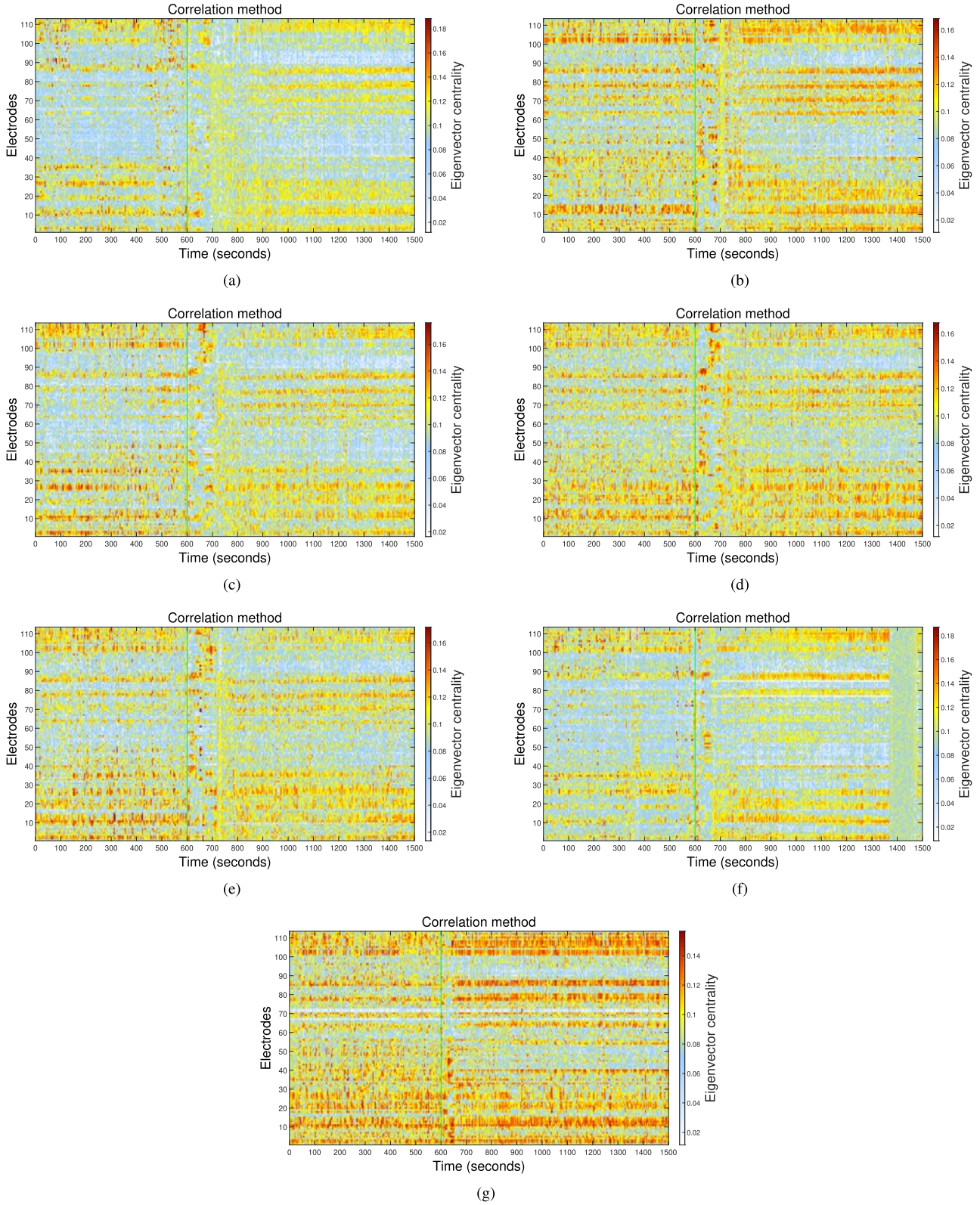


**FIGURE 3.** EC plots for the correlation method for clinical ((a)-(e)) and subclinical ((f)-(g)) seizures in patient 1. Green lines in all plots denote the seizure onset time.

heterogeneity (DH) was calculated for the preictal periods for all seizures in each patient.

Higher DH of applying SLRPM in comparison to the SRPM and correlation methods underscores the importance

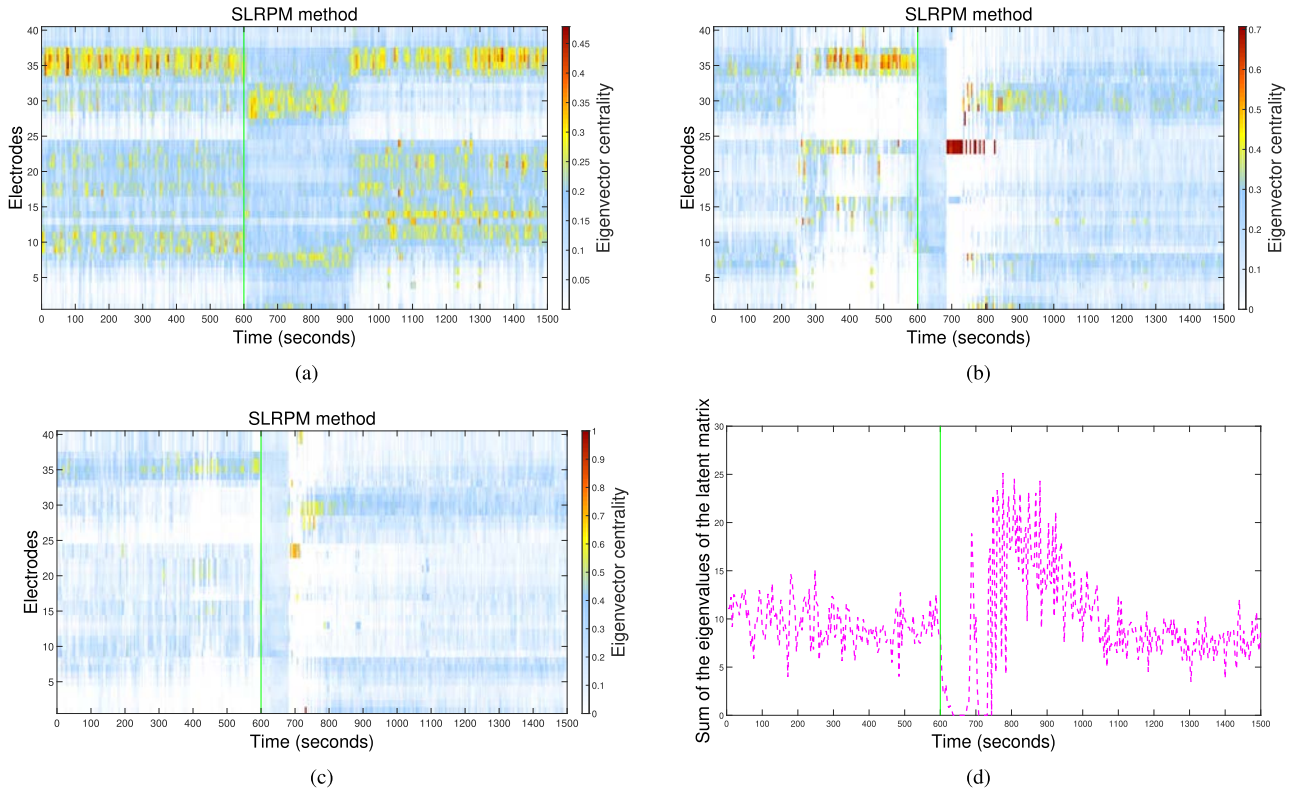


**FIGURE 4.** EC plots for the SLRPM method for seizures in patient 4. Also shown is the plot (d) of the latent inputs estimated by the SLRPM method for one example seizure (corresponding to panel (b)) in patient 4. Green lines in all plots denote the seizure onset time.

**TABLE 1.** Heterogeneity statistics for seizures in each patient for the SLRPM, SRPM, and correlation methods.

| Patient ID | DH for SLRPM | A/O for SLRPM | DH for SRPM | A/O for SRPM | DH for correlation | A/O for correlation |
|---|---|---|---|---|---|---|
| 1 | 68.51 | 0/10 | 55.42 | 0/10 | 5.93 | 0/10 |
| 2 | 42.51 | 7/9 | 31.17 | 6/9 | 2.08 | 0/9 |
| 3 | 30.99 | 2/10 | 18.04 | 3/10 | 6.27 | 0/10 |
| 4 | 4.89 | 0/2 | 9.93 | 0/2 | 0.30 | 0/2 |
| 5 | 32.05 | 4/9 | 11.76 | 0/9 | 2.92 | 0/9 |
| 6 | 15.96 | 1/12 | 10.61 | 1/12 | 3.63 | 1/12 |
| 7 | 21.72 | 1/13 | 10.43 | 1/13 | 7.24 | 3/13 |
| 8 | 48.10 | 1/6 | 25.48 | 3/6 | 1.72 | 0/6 |
| 9 | 53.37 | 12/28 | 35.53 | 6/28 | 13.31 | 17/28 |
| 10 | 57.53 | 0/8 | 36.50 | 2/8 | 4.45 | 0/8 |
| 11 | 11.32 | 0/8 | 8.85 | 0/8 | 6.31 | 0/8 |
| 12 | 24.02 | 0/4 | 18.36 | 0/4 | 2.67 | 0/4 |

of taking the latent inputs into consideration while estimating connectivity of brain regions. In other words, the relatively low DH in the SRPM and correlation methods is attributable to the common latent inputs. Few of the active electrodes estimated by the SLRPM method correspond to the onset channels. The activity in the other channels may (1) represent activity that leads the seizures, (2) be necessary for the seizure to start without having involvement per se (e.g. a permissive role), and/or (3) provide background inputs that are sufficient to maintain a seizure. Despite the fact that all the patients included in the study had the same epilepsy type, namely complex partial epilepsy, the DH estimated by SLRPM covered a relatively wider range. This indicates that the preictal cortical connectivity across seizures, after excluding the effect of the common latent inputs, can be highly heterogeneous. We also did not find any obvious age or sex related differences from the DH values estimated by the SLRPM method, i.e., both high and low DH values were present across genders and ages. This is consistent with previous findings [43], which suggest that there are no gender- or age-related differences as far as partial seizures are concerned.

Some prior research has shown that there is desynchronization among neurons in the preictal period of seizures in both human [4], [5] and animal [44] models of epilepsy. However, in these studies, there is an implication that

this desynchronization is consistent across seizures and the variability of the preictal dynamics across seizures within patients was not rigorously studied. Ours may be the first study addressing this important question. Recent research [40], [45], [46] has suggested that seizures originate due to the complex interplay of excitatory and inhibitory neurons in the preictal period. This interplay of excitatory and inhibitory neurons which leads to seizure generation has also been confirmed in simulation models of seizures [47]. By including both homogeneous and heterogeneous connectivity in their models, the authors were able to reproduce the spatiotemporal dynamics of seizure generation in patients with partial epilepsy. The presence of higher levels of inhibitory activity could possibly induce more variability or heterogeneity, which in turn could lead to less seizure severity. Hence the relatively low correlation between DH and seizure severity estimated by SLRPM and SRPM methods are consistent with clinical implications, whereas results from the correlation method, which did not directly model the latent inputs, have the wrong clinical implication. Even though this inhibitory hypothesis is one possible explanation of the low correlation between DH and seizure severity estimated by SLRPM and SRPM methods, we cannot rule out the possibility of other complex mechanisms, discussion of which is beyond the scope of this paper.

One of the limitations of our study is that we assumed the preictal periods to be the same (10 minutes) across seizures and patients. However, the preictal period can be highly variable from seizure-to-seizure within and across patients [48] and is, in fact, ill-defined. In order to rigorously characterize the preictal periods, comparison of the preseizure dynamics with that from interictal periods is necessary [48]. Such an analysis is, however, beyond the scope of this paper and is a topic for future research. Moreover, we have focused our analysis on braodband power rather than individual frequency bands (delta, theta, alpha, beta, and gamma). Such an analysis was motivated by prior work on epileptic seizures showing that most preictal dynamics are common, at least to some extent, across frequency bands [49], enabling us to capture the most salient and reproducible preictal dynamics across all frequency bands.

Even though SLRPM provides a way to visualize the local cortical connectivity by conditioning on the latent inputs, it is worth highlighting some of its limitations, which mainly arise due to its assumptions on the statistics and structure of the signal (ECoG recordings). The assumption of Gaussian-distributed signal need not always hold true for cortical activity [50]. However, previously we have shown that [25] the SLRPM method is robust to the distribution of signals in artificial networks. Moreover, the assumptions of sparsity of observed variables (in this case, the ECoG recordings) and low rankness of the latent inputs need not always hold true for an epileptic brain. In our prior work [25], we also have shown that SLRPM performs well for a wide range of non-sparse and non-low rank signals using simulations of artificial networks. Furthermore, even though SLRPM is a linear method, it is able to perform well in the presence of nonlinearity [25], which is often the nature of neural dynamics. The robustness of SLRPM method to its intrinsic assumptions on the statistics and structure of the ECoG recordings makes it an attractive way to analyze seizure dynamics and brain connectivity more generally.

Despite these limitations, we have shown that a network-based approach can be used to probe the underlying spatiotemporal preictal dynamics of epileptic seizures. For the first time, we have been able to rigorously characterize local cortical activity while simultaneously removing the effects of the latent inputs. Methods such as the correlation or the Granger causality, which are widely used in neuroimaging studies do not explicitly model the latent inputs and can estimate spurious connectivity in the presence of common latent inputs. Calculating the conditional statistics of brain connectivity, we have shown that there can be a very wide range of degree of heterogeneity across patients and suggests the critical role of inhibitory neurons for generalization of seizures. This might open up alternating novel approaches for predicting and controlling seizures.

## V. CONCLUSION

Preictal global spatiotemporal dynamics and its intra-patient variability in the epileptic human brain is an important area of research, a better understanding of which has the potential to devise practicable seizure prediction algorithms. To address this challenge, we adopted a network based approach and analyzed preictal broadband brain connectivity from human ECoG recordings. Since ECoG electrodes record from only a part of the cortex, brain connectivity was therefore estimated using the SLRPM method, which calculates connectivity from partial correlations of the conditional statistics of the observed regions given the unobserved latent regions. Results from the SLRPM method were compared to those from the SRPM and correlation methods, which do not account for the unobserved inputs when estimating brain connectivity. We found that the degree of heterogeneity estimated by the SLRPM method was higher than those estimated by the SRPM and correlation methods for the preictal periods in most patients. These results reveal substantial heterogeneity among brain areas in the preictal period of human epileptic seizures. Moreover, the correlation between the degree of heterogeneity and seizure severity of patients for SLRPM and SRPM methods were lower than that obtained from the correlation method, supporting recent findings which suggest that inhibitory neurons can have anti-seizure effects by inducing variability or heterogeneity across seizures. Understanding how this variability is linked to seizure initiation may lead to better predictions and controlling therapies.

## CONFLICT-OF-INTEREST STATEMENT

Due to HIPPAA regulations and other research protocols involved, we are unable to make the dataset used in this study publicly available at this time.

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**ANUP DAS** received the B.Tech. degree in electronics and communication engineering from IIT at Guwahati, India, in 2013, and the M.S. and Ph.D. degrees in electrical engineering (signal and image processing) from the University of California at San Diego, in 2015 and 2018, respectively. Since April, 2018, he has been a Postdoctoral Research Fellow with the Stanford Cognitive and Systems Neuroscience Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University. His current research interest is in computational cognitive neuroscience in which he develops and applies advanced signal processing methods for analyzing the humanbrain. He received the University of California, San Diego Electrical and Computer Engineering Departmental Fellowship, in 2013. More details about him can be found from his webpage http://web.stanford.edu/ a1das/.

**SYDNEY S. CASH** received the M.D. and Ph.D. degrees from Columbia University, New York.

He is currently an Associate Professor with the Epilepsy Division, Neurology Department, Massachusetts General Hospital (MGH), and also with Harvard University. He then moved to Boston for neurological training. He stayed at MGH for further training in epilepsy and neurophysiology during the Research Fellowship funded by the American Epilepsy Society and the Grass-Morison Fellowship. His research in his lab is, broadly speaking, dedicated to trying to understand normal and abnormal brain activity, particularly oscillations, using multimodal and multiscalar approaches. Specifically, his group combines novel microelectrode approaches with invasive and non-invasive techniques, such as electroencephalography and magnetoencephalography to record directly from human and animal cortex, and subcortical structures. One part of the lab studies the neurophysiology of epilepsy, trying to understand how seizures start and stop, and how they might be predicted and terminated. These questions overlap with investigations into the mechanisms of sleep, normal language, auditory, and other cognitive processing. The laboratory also focuses on the development of novel neurotechnological approaches to develop neuroprosthetic devices which can help diagnose and treat common and devastating neurological diseases. He is a member of the BrainGate Clinical Trial Team. He is also the Co-Director of the Department of Neurology Center for Neurotechnology and Neurorecovery.

**TERRENCE J. SEJNOWSKI** (Fellow, IEEE) received the Ph.D. degree in physics from Princeton University. He is currently an Investigator with the Howard Hughes Medical Institute, a Distinguished Professor with the University of California at San Diego, and holds the Francis Crick Chair at the Salk Institute. He is a pioneer in computational neuroscience and his goal is to understand the principles that link brain to behavior. His laboratory uses experimental and modeling techniques to study the biophysical properties of synapses and neurons, and the population dynamics of large networks of neurons. He has published over 500 scientific articles and 14 books, including *The Computational Brain*. He is the President of the Neural Information Processing Systems (NIPS) Foundation and the premier Conference on Machine Learning and Neural Computation. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the National Academy of Engineering. He was instrumental in shaping the BRAIN Initiative that was announced by the White House, in 2013. He has served on the Working Group of the Advisory Committee to the Director of NIH for the BRAIN Initiative.