JNS

CLINICAL ARTICLE

J Neurosurg 126:2036–2044, 2017

Prediction and detection of seizures from simultaneous thalamic and scalp electroencephalography recordings

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OBJECTIVE The authors explored the feasibility of seizure detection and prediction using signals recorded from the anterior thalamic nucleus, a major target for deep brain stimulation (DBS) in the treatment of epilepsy.

METHODS Using data from 5 patients (13 seizures in total), the authors performed a feasibility study and analyzed the performance of a seizure prediction and detection algorithm applied to simultaneously acquired scalp and thalamic electroencephalography (EEG). The thalamic signal was obtained from DBS electrodes. The applied algorithm used the similarity index as a nonlinear measure for seizure identification, with patient-specific channel and threshold selection. Receiver operating characteristic (ROC) curves were calculated using data from all patients and channels to compare the performance between DBS and EEG recordings.

RESULTS Thalamic DBS recordings were associated with a mean prediction rate of 84%, detection rate of 97%, and false-alarm rate of 0.79/hr. In comparison, scalp EEG recordings were associated with a mean prediction rate of 71%, detection rate of 100%, and false-alarm rate of 1.01/hr. From the ROC curves, when considering all channels, DBS outperformed EEG for both detection and prediction of seizures.

CONCLUSIONS This is the first study to compare automated seizure detection and prediction from simultaneous thalamic and scalp EEG recordings. The authors have demonstrated that signals recorded from DBS leads are more robust than EEG recordings and can be used to predict and detect seizures. These results indicate feasibility for future designs of closed-loop anterior nucleus DBS systems for the treatment of epilepsy.

https://thejns.org/doi/abs/10.3171/2016.7.JNS161282

KEY WORDS epilepsy; thalamic DBS; deep brain stimulation; prediction; detection; EEG; closed-loop feedback

Among the 2 million patients living with partial onset epilepsy in the United States, approximately 400,000 have refractory epilepsy.[2,10,21] Since only a minority of these patients are eligible for resective surgery, about 1500 undergo resection annually.[3] This leaves a major unmet need of alternate treatments for refractory epilepsy.[16] Some of these patients can be considered for neuromodulation with thalamic stimulation, responsive stimulation of the seizure focus, or cranial nerve stimulation (e.g., vagus nerve stimulation).[8] The first report of anterior nucleus thalamic deep brain stimulation (DBS) dates back to the 1980s.[36] Several initial case series[1,9,11,14,20,27,33,35] led to a multicenter, randomized controlled trial (SANTE trial) demonstrating a significant and sustained efficacy of anterior nucleus DBS.[7,31]

Anterior nucleus DBS currently involves a duty cycle with stimulation on for 1 minute and off for 4 or 5 minutes irrespective of seizure onset.[15] With the approval of a re-

ABBREVIATIONS DBS = deep brain stimulation; EEG = electroencephalography; LFP = local field potential; ROC = receiver operating characteristic; SI = similarity index.

SUBMITTED May 18, 2016. **ACCEPTED** July 27, 2016.

INCLUDE WHEN CITING Published online October 7, 2016; DOI: 10.3171/2016.7.JNS161282.

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sponsive neurostimulation system (Neuropace Inc.), there is renewed interest in exploring the feasibility of seizure prediction from thalamic recordings and potentially devising a closed-loop stimulation system.[24] Initial evidence suggests that seizures can be detected earlier from thalamic local field potentials (LFPs) than from scalp electroencephalography (EEG).[25] We have extended these preliminary findings in a series of patients with nonresective yet primarily partial epilepsy who underwent anterior nucleus DBS. We used a nonlinear method of predicting seizures by comparing similarity index (SI) between a reference window and the peri-ictal recordings.[17] We hypothesize that thalamic recordings result in earlier and more accurate seizure identification.

Methods

This study was approved by the University Health Network Research Ethics Board.

Study Patients

We recorded simultaneous scalp and thalamic EEG in 5 patients with medically intractable epilepsy who underwent anterior nucleus DBS between 2009 and 2013 (Table 1 and Supplementary Table 1). Results from these patients' EEG recordings have not been previously reported. Our technique for DBS implantation was previously published.[11] Briefly, patients underwent stereotactic frame placement either awake or under anesthesia. MRI was performed with the frame in place. We chose a trajectory to place all 4 contacts of the Medtronic 3387 stimulating lead (4 contacts each 1.5 mm long and 1.5 mm apart) within the thalamus. This invariably resulted in placement of the 2 superficial contacts (Contacts 3 and 2) within the anterior nucleus and the 2 deep contacts in the dorsomedial nucleus (Contacts 1 and 0). The placement of DBS electrodes was confirmed by postoperative MRI. Simultaneous scalp and thalamic EEG recordings were obtained in an epilepsy monitoring unit with externalized DBS leads for a period of 3–7 days before internalization and implantation of pulse generators. The data from these recordings were stored in an offline server and can be accessed in entirety for future review.

For control data, EEG results were obtained from DBS electrodes implanted in the subthalamic nucleus (STN) of patients with Parkinson's disease with no seizure history. LFP signals from the STN were recorded in 3 patients who underwent staged DBS implantation including an interval with externalized DBS leads.

Signal Acquisition and Processing—Thalamic LFPs and Scalp EEG

The scalp EEG was recorded from 27 electrodes, including the standard international 10–20 system electrode positions plus F9/10, T9/10, P9/10, and zygomatics (Sp1/2). The thalamic LFP recordings were obtained from all 8 contacts of externalized DBS leads (RAN0, RAN1, RAN2, RAN3, LAN0, LAN1, LAN2, and LAN3). The recordings were digitally acquired at sampling frequencies of 256–1024 Hz (XLTEK, Natus Medical Inc.). Bipolar signals (6 pairs—RAN0–RAN1; RAN1–RAN2; RAN2–RAN3; LAN0–LAN1; LAN1–LAN2; and LAN2–LAN3) were derived from the monopolar DBS recordings to ensure that only "local" thalamic signals were considered, and also to allow fair comparison between DBS recordings and bipolar signals from the scalp EEG recordings. All signals were high pass filtered with a cutoff frequency of 0.5 Hz, and a 10-bin smoothing was applied (Fig. 1A).

TABLE 1. Clinical characteristics and outcomes of the study cohort

Pt	Age (yrs), Sex	No. of Szs Recorded	Type of Epilepsy	Clinical Outcome After AN DBS
A	27, F	7	Partial epilepsy, lt hemispheric cortical dysplasia	68% reduction in Sz frequency at 3 yrs
B	23, M	2	Partial epilepsy, lt perisylvian microgyria, periventricular heterotopia	83% reduction in Sz frequency at 1.5 yrs
C	16, M	2	Partial epilepsy, postencephalitic, frontal predominance	90% reduction in Sz frequency at 1 yr
D	42, M	1	Symptomatic generalized epilepsy, Lennox-Gastaut syndrome	80% reduction in Szs at 1.3 yrs
E	28, F	1	Partial epilepsy, lt temporal	37% reduction in Sz frequency; removal at 3 yrs

AN = anterior nucleus; Pt = patient; Sz = seizure.

Seizure Detection and Identification of EEG Segments for Analysis

Artifact-free EEG was identified by an expert epileptologist (R.A.W.) for visual determination of times of electrographic seizure onset. The simultaneous video data were also analyzed for clinical corroboration. A recording epoch of 10–30 minutes before each seizure onset and 10–30 minutes after each seizure onset were extracted for analysis. A total of 13 seizure episodes were manually detected in the 5 patients.

Calculation of SI

We used a modified calculation of the SI[19] that has been shown to be more robust, with a lower false-alarm rate compared with the original SI calculation presented by Le Van Quyen et al.[17] The exact formulas have been described in detail by Li and Ouyang.[19] Briefly, the steps are as follows: 1) Positive zero-crossings during a test window (30 seconds of data) were used to determine a series of time intervals (I_n). 2) A phase space A_{test} was reconstructed for I_n with dimension m = 10 ($A_{test} = I_n, I_{n-1}, \ldots, I_{n-m+1}$, where I_n is an embedded scalar time series into an m dimensional space[19]). 3) This matrix A_{test}, as well as the reference matrix A_{ref} (calculated using time intervals from a 2.5-minute reference window), are projected onto the principal axes of the reference window through a singular value decomposition, yielding projection matrices X_{test} and X_{ref} (Fig. 1B). 4)

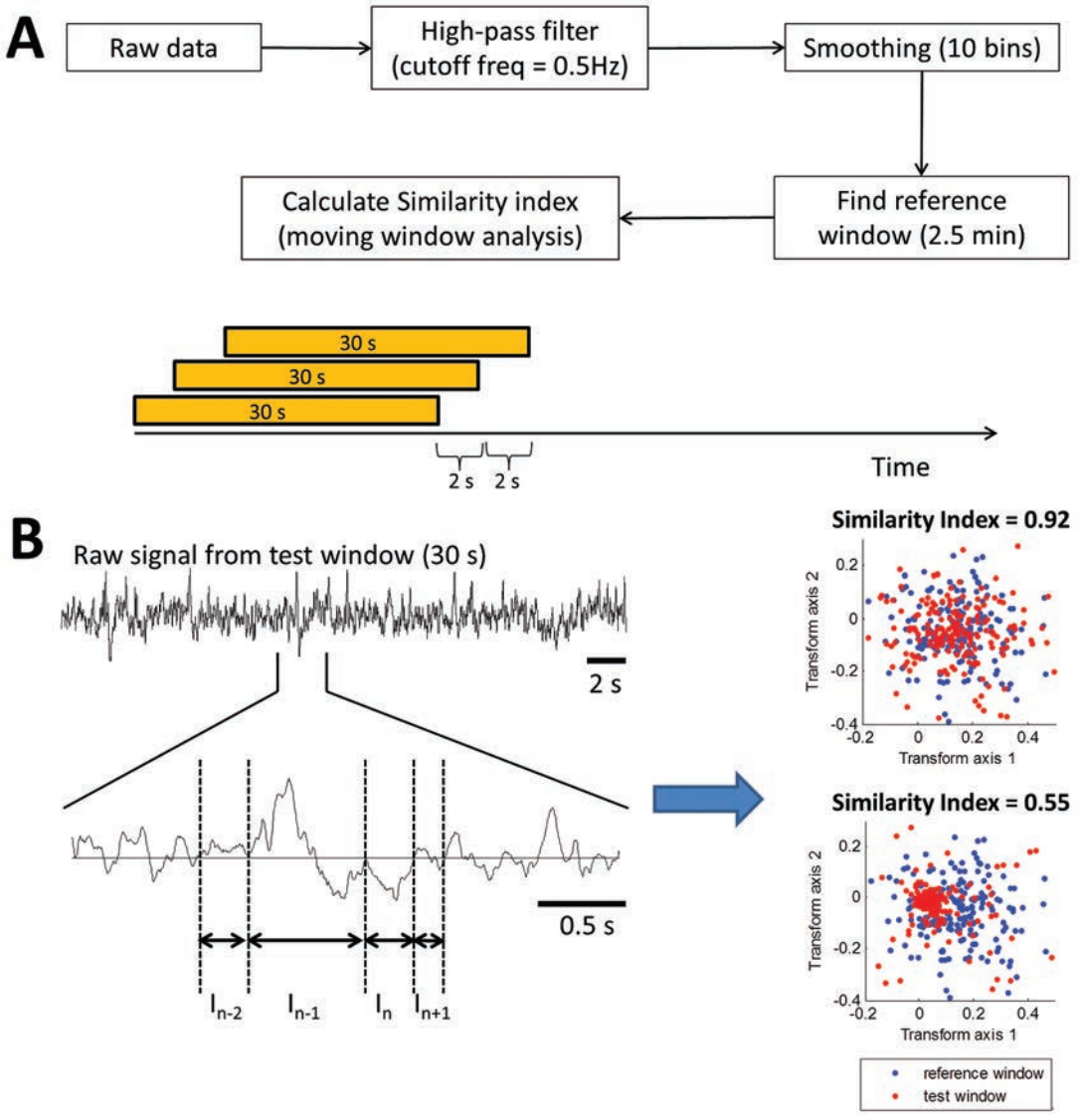

FIG. 1. Method used in signal processing and analysis. **A:** Block diagram showing steps for signal processing. **B:** Example test window showing the steps involved in the calculation of the SI. Two examples are shown for the projection of the time series onto the first 2 transform axes, resulting in one high SI value and another moderate SI value. Figure is available in color online only.

The SI is calculated as the ratio between the cross-correlation integral (C_{cross}) and the autocorrelation integrals (C_{auto}) of X_{test} and X_{ref}.

$$SI = \frac{C_{cross}\,(X_{test}, X_{ref})}{\sqrt{C_{auto}\,(X_{test}, X_{test}).\,C_{auto}\,(X_{ref}, X_{ref})}}$$

The SI has a range from 0 to 1. If the reference window and test window have similar underlying dynamics, the SI will be close to 1; otherwise, a decrease in SI indicates a change in dynamics between the test window and the reference window. The SI was calculated every 2 seconds, using a 30-second moving test window (Fig. 1A). For the reference window, we selected a 2.5-minute window prior to the epilepsy onset that had the minimum signal standard deviation, therefore representing a period of quiescence during the recording. For each patient, the reference window was located at least 20 minutes prior to the onset of the first seizure episode. If there was more than 1 seizure episode in a day, the reference window was updated during the interictal period if 2 consecutive seizures occurred more than 90 minutes apart.

Prediction/Detection of Seizure

We defined an "alarm," indicating a possible seizure, to have occurred when the SI for a selected channel dropped below a certain threshold for a minimum of 10 seconds. A minimum threshold-crossing time of 10 seconds was chosen so that random fluctuations in SI would not result in false alarms. For each patient, detection and false-alarm rates were calculated for all channel and threshold combinations, in intervals of 0.01. A specific threshold and channel were selected for each patient such that the differ-

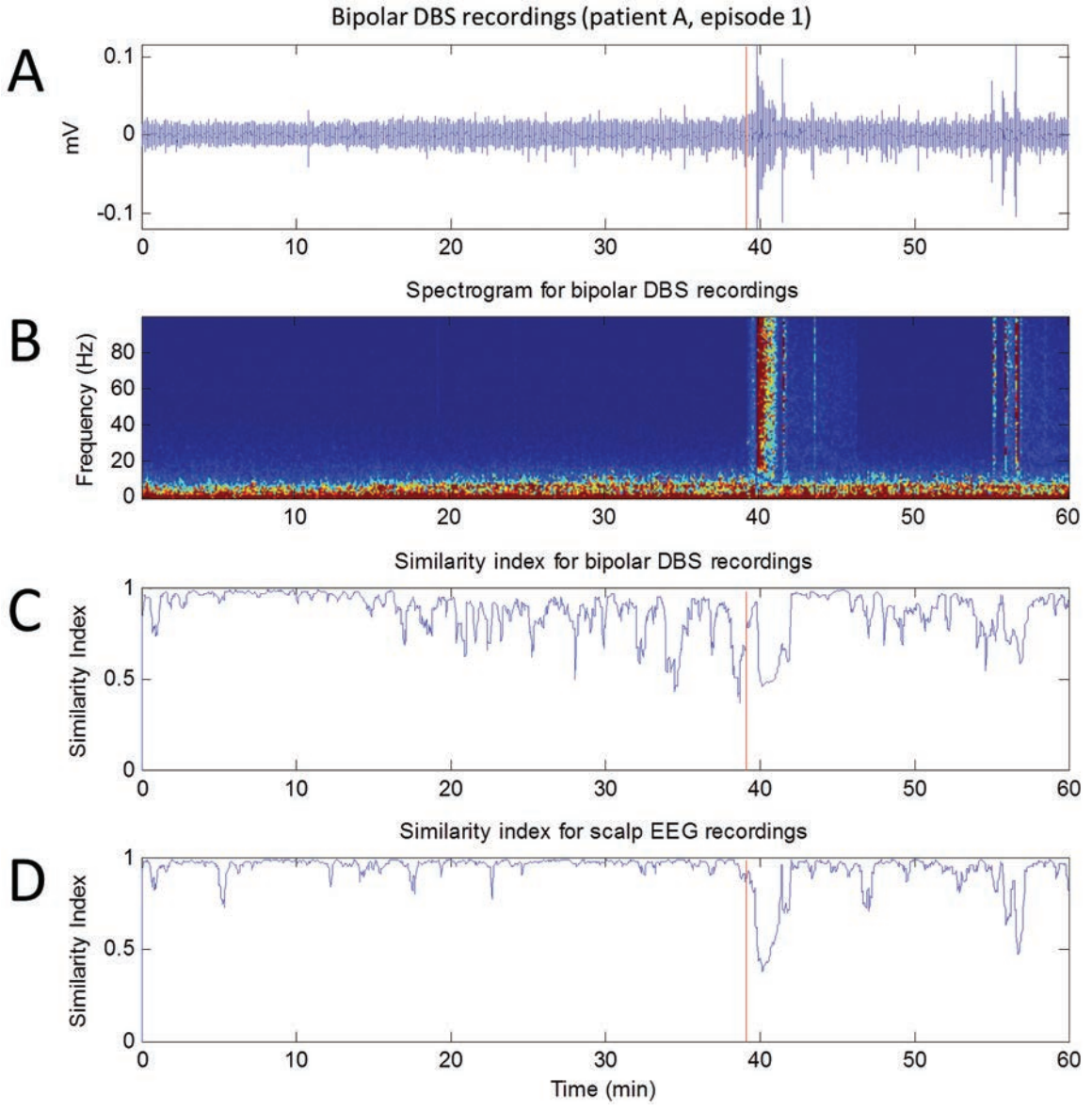

FIG. 2. Patient A. Example recording segment and analysis. **A:** Raw recordings from one bipolar thalamic DBS channel A. Seizure onset is indicated by the *red vertical line*. **B:** Spectrogram for recording in panel A. **C:** SI calculated for recording in panel A. A decrease in SI is seen before the onset of seizure. **D:** SI for a scalp EEG channel. No apparent decrease in SI is observed before seizure onset, but SI decreases sharply after seizure onset. Figure is available in color online only.

ences between detection rates and false-alarm rates were maximized.

Alarms were classified as follows: true prediction, alarm between –10 minutes and seizure onset; true detection, alarm between –10 minutes and 10 minutes after seizure onset; false alarm, all other alarm times; and misses, no alarm between –10 minutes and 10 minutes after seizure onset.

Prediction and detection rates were calculated as the ratio between the number of seizures predicted or detected and the total number of seizures. The false-alarm rate was defined as the number of false alarms per hour. Since the false-alarm rate for each patient varies considerably, a normalized false-alarm rate was used to allow comparison across patients. The normalized false-alarm rate was calculated as the ratio between the false-alarm rate and the maximum possible false-alarm rate using the highest threshold.

Results

The SI was calculated for both thalamic DBS and scalp EEG recordings during 13 seizures. In some seizures, we observed a decrease in the SI only in the thalamic LFP signals prior to the onset of seizure (Fig. 2C). In these seizures, no pre-ictal change in SI was observed in the scalp EEG signals (Fig. 2D), nor was any change apparent in the raw data or power spectrum data prior to the seizure onset (Fig. 2A and B). In other seizures, changes in SI were observed in both thalamic DBS and scalp EEG recordings.

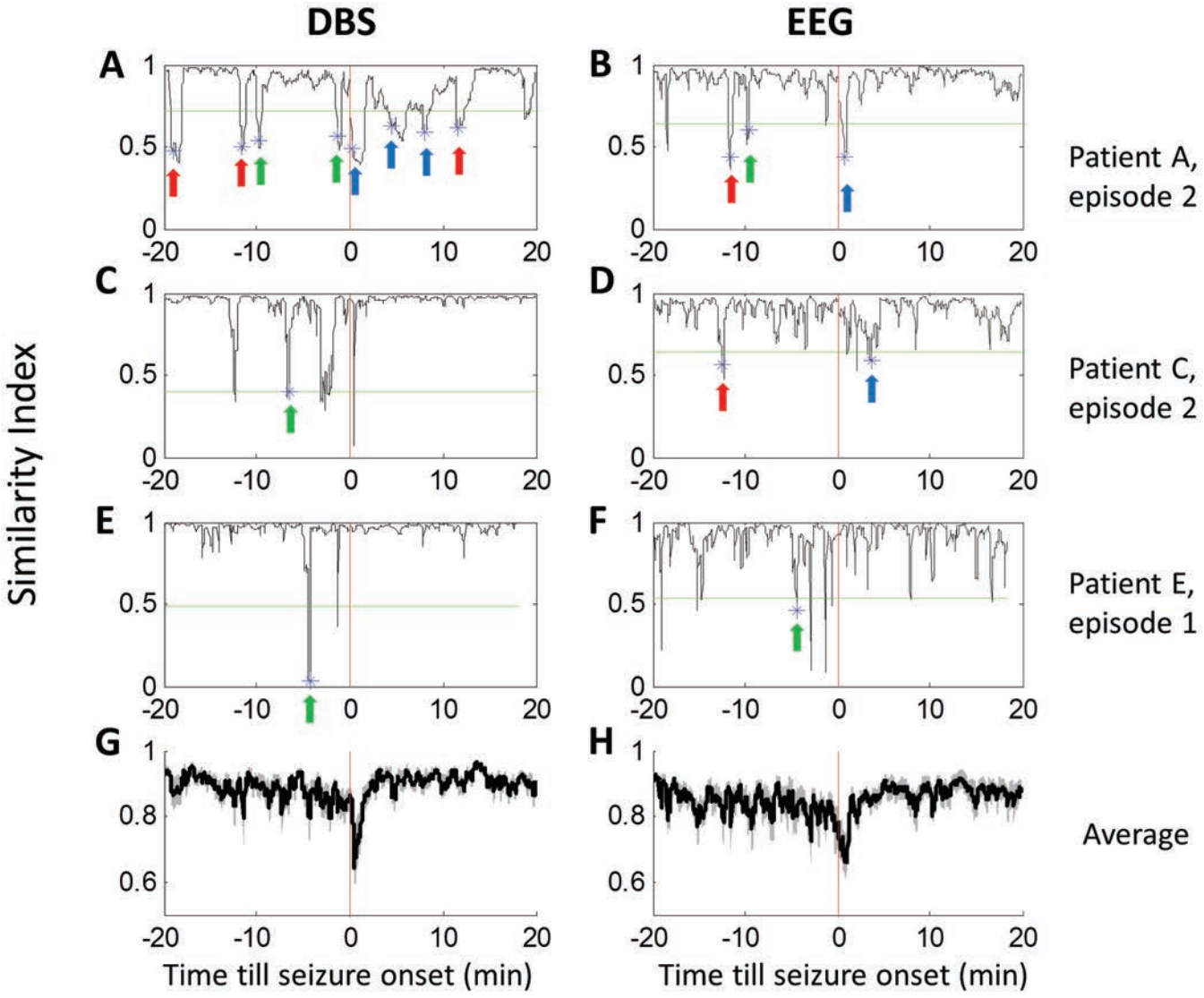

FIG. 3. Examples of prediction, detection, and false alarm. **A–F:** Examples of true prediction (*green arrow*), true detection (*blue arrow*), and false alarm (*red arrow*) for 3 patients using thalamic DBS recordings (A, C, and E) and scalp EEG recordings (B, D, and F). The *red vertical line* represents seizure onset time; the *green horizontal line* represents threshold for alarm. **G and H:** The mean SI for DBS and EEG recordings. Figure is available in color online only.

Some examples of prediction, detection, and false alarms from SI information calculated using both EEG and DBS signals obtained in 3 patients are shown in Fig. 3. The mean SI values from all 13 seizure episodes (Fig. 3G and H) show that a decrease in the SI is observed directly following the seizure onset for both DBS electrode and scalp EEG recordings. However, a decrease in SI prior to seizure onset is not apparent from the mean SI values, indicating that the profile for changes in SI prior to seizures is not uniform across all patients or seizures.

Table 2 presents the compiled results for all 13 seizures, showing the earliest alarm times for each seizure, as well as the prediction rate, detection rate, and average false-alarm rate for each patient. These values were based on patient-specific optimized selections of channels and thresholds for both DBS electrode and scalp EEG recordings. From DBS recordings, 10 of 13 seizures were predicted, with a mean prediction rate of 84.28% ± 10.2% (± SE); and 12 of 13 seizures were detected, with a mean detection rate of 97.14% ± 2.86%. On average, the alarm was triggered 4.59 ± 1.17 minutes prior to seizure onset. In comparison, for scalp EEG recordings, 8 of 13 seizures were predicted, with a mean prediction rate of 71.42% ± 19.69%; all 13 seizures were detected, with a detection rate of 100%. On average, the alarm was triggered 2.04 ± 1.45 minutes prior to the onset of seizure.

To test the robustness and to get a global view of the differences in performance between DBS and EEG recordings, we used a range of thresholds and all possible contacts to generate receiver operating characteristic (ROC) curves for each patient. These curves compare detection and prediction rates against false-alarm rates; Fig. 4 shows the averaged ROC curves across all patients. For both detection and prediction, DBS recordings outper-

TABLE 2. Alarm timings and prediction, detection, and false-alarm rates for each patient

		Thalamic DBS				Scalp EEG			
Sz No.	Pt	Earliest Alarm (min)	Prediction Rate (%)	Detection Rate (%)	False-Alarm Rate (no./hr)	Earliest Alarm (min)	Prediction Rate (%)	Detection Rate (%)	False-Alarm Rate (no./hr)
1	A	−6.88	71.4	85.7	3.55	0.88	57.1	100	3.91
2	A	−9.80				−9.63			
3	A	0.38				6.78			
4	A	NA				0.87			
5	A	−0.13				−0.27			
6	A	−0.62				−0.62			
7	A	−8.82				−8.75			
8	B	−1.83	100	100	0	−7.00	100	100	0
9	B	−8.63				−0.03			
10	C	0.63	50	100	0.38	1.10	0	100	1.13
11	C	−6.58				3.62			
12	D	−8.50	100	100	0	−9.13	100	100	0
13	E	−4.32	100	100	0	−4.32	100	100	0
Mean		−4.59	84.28	97.14	0.79	−2.04	71.42	100	1.01
SE		1.17	10.20	2.86	0.69	1.45	19.69	0	0.76

NA = not available.
Thalamic DBS predicted 10 of the 13 seizures, detected 12, and missed 1. Scalp EEG predicted 8 of the 13 seizures, detected 13, and missed 0.

formed EEG recordings, with higher detection and prediction rates achievable using DBS signal at any selected threshold. It is interesting to note from the ROC curves that across all channels and all patients, application of the algorithm to both DBS and scalp EEG signal performed better than chance for seizure detection (detection rates are higher than false-alarm rates, Fig. 4A), but for the prediction of seizures, the discriminatory ability of scalp EEG, when considering all channels, is almost no better than chance (prediction rate almost the same as the false-alarm rate, Fig. 4B).

Finally, analysis of control data shows that SI stayed very high (> 0.9) for all 3 control data sets (Supplementary Fig. 1), confirming that SI is a reliable measure for the dynamical changes underlying brain activities in epilepsy patients.

Discussion

To our knowledge, this is the first report of the use of SI to detect changes in the underlying dynamics in simultaneous thalamic and scalp EEG recordings. We showed that through optimized selection of channels and thresholds, seizure detection and prediction, with low false-alarm rates, can be achieved using both thalamic and scalp EEG. In general, thalamic DBS signals resulted in earlier seizure detection and a higher prediction rate. When averaged across all patients, channels, and thresholds, DBS outperforms EEG recordings for both detection and prediction. This suggests that the DBS recordings resulted in more robust seizure detection/prediction compared with EEG recordings.

Thalamic Versus Scalp EEG

There may be a number of reasons behind the superior seizure detection and prediction with thalamic compared with scalp EEG recordings. First, partial onset seizures (e.g., limbic origin) may propagate to the thalamus before propagation to the cortical surface, resulting in earlier changes in the neural dynamics within the thalamus compared with the cortex. Second, the DBS electrode contacts are physically located closer together compared with scalp EEG electrodes, and by using bipolar recordings, a small area of thalamic neural activity is being captured through DBS electrode contacts, whereas scalp EEG monitors the combined activity from a larger and less specific area of cortical activity underneath the electrodes. Lastly, and most importantly, DBS electrodes are in direct contact with brain tissue, whereas EEG electrodes are situated above the scalp. Therefore, neural signals recorded by the scalp EEG may be more attenuated and have a lower signal-to-noise ratio since electrical activity has to pass through several layers of fluid, bone, and soft tissue before reaching the electrodes.

Comparison With Previous Results

The main novelty in this analysis involves the comparison of the seizure prediction/detection rates from simultaneously recorded thalamic DBS and scalp EEG signals. Most previous studies have focused on using only scalp EEG,[32,34] only intracranial EEG,[4,5,12,13,22,25,26,28] or only thalamic DBS signals.[25] One study compared scalp EEG and nonthalamic intracranial EEG for predicting seizures and found little difference between the 2 signals.[18]

Our prediction rate (84.28%), detection rate (97.14%), and mean false-alarm rate (0.79/hour) from DBS signals, using optimized patient-specific channel and threshold selection, are comparable to other studies.[4,12,18,22,23,25,26,28,32,34] However, it is important to keep in mind that the defini-

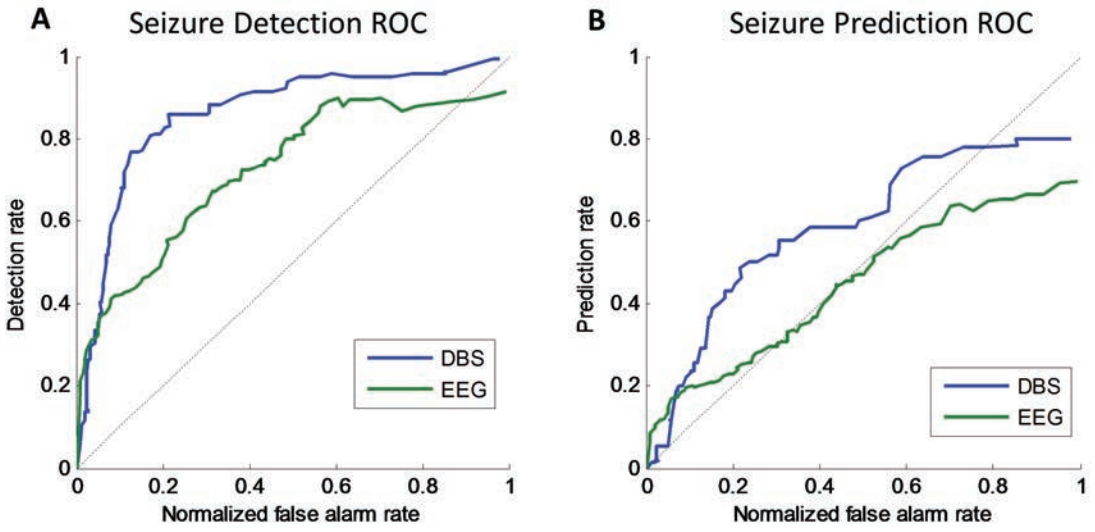

FIG. 4. ROC curves for detection (**A**) and prediction (**B**) of seizures. ROC curves for DBS are above those for EEG, indicating better algorithm performance with thalamic DBS recordings. Figure is available in color online only.

tions of "true prediction" and "false alarm" vary greatly across studies. For example, Shahidi Zandi et al.[34] defi ed an alarm to be true if a seizure occurred within 40 minutes after the alarm; Ozdemir and Yildirim[28] defined a prediction to be correct if a seizure occurred between 5 and 35 minutes after the alarm; while Iasemidis et al.[12] used a 3-hour allowable predictive horizon. We implemented a short prediction time frame (true prediction defined as seizure within 10 minutes after alarm), so that each alarm does not trigger an extended period of "warning." For a potential closed-loop DBS system, a shorter period of stimulation would also be more advantageous in terms of battery savings, and 10 minutes of stimulation prior to seizure onset is an acceptable period.

The predictive timeframe reported in the past ranges from a few seconds[25,26,32] to minutes[5,29,34] to hours[12,22,23] before seizure onset. Another study using a different seizure detection algorithm applied to thalamic DBS signals[25] showed that seizures could be detected on average 2–20 seconds after electrographic onset, and between 0.5 and 3 seconds before onset of the clinical seizure. This timeframe is considerably shorter compared with our seizure prediction results. For warning purposes, a few seconds of alarm may not be enough time to ensure that the patient is brought to a safe location before the onset of the clinical seizure.[4] With DBS, it may also take longer than a few seconds for the stimulation to take effect. Therefore, an alarm that has a predictive horizon on the order of minutes is preferred. However, the predictive horizon should also not be on the order of hours for reasons stated above.

Clinical and Biological Relevance

From a clinical perspective, these results demonstrate the feasibility of using thalamic EEG as a biomarker for seizure prediction in future closed-loop systems. Closed-loop DBS for seizure control may improve efficacy of DBS, and would also greatly reduce power consumption, hence increasing the lifespan of batteries and reducing the need for frequent surgeries to replace batteries. An implanted seizure advisory system using intracranial EEG signals with long-term recording capabilities has already been demonstrated,[4] and it is conceivable that a similar system can be implemented with current DBS systems for treatment of epilepsy.

Our results show that seizures can be detected earlier from thalamic compared with scalp EEG recordings. Physiologically this may reflect the role of the thalamus in seizure pathophysiology, especially initiation and propagation.[6,29,30] However, it is important to note that not all seizures were detected earlier in the thalamus. Of 13 seizures, only 6 were detected considerably (more than 1 minute) earlier than scalp recordings. In Patient C with generalized onset seizures, thalamic EEG outperformed scalp EEG for seizure prediction (lead time 0.63 and −6.58 minutes vs 1.1 and 3.62 minutes). Although the sample size in this study is small, heterogeneity can already be observed, showing that the mechanisms and dynamics of seizures across patients and even within the same patient can be different. The relationship between seizure prediction/detection and seizure type, location of seizure onset zone, and other clinical characteristics (e.g., response to DBS) can be investigated in future studies with larger cohorts.

Limitations and Future Directions

The biggest limitation of this study is the amount of seizure data, which did not allow us to use different sets of data for selection of optimal parameters and testing. As such, the prediction and detection rates using optimized threshold and channel selection may be biased. We attempted to mitigate this bias partially by comparing the averaged ROC curves when using all possible channel and threshold selections. Future prospective experimental design would involve long-term data collection and use separate data sets for training and testing. Nonetheless, our comparative analysis of DBS electrode and scalp EEG recordings for seizure prediction and detection is valid since these recordings were acquired simultaneously.

In this study, we only used a single channel and 1 param-

eter (SI) to determine alarm times. Future analysis would consider multichannel activity, and SI values could be used in conjunction with other parameters, such as spectral power, to achieve higher degrees of accuracy in prediction. Machine learning methods could be employed to extract optimal features for classification in such analyses.

The choice of reference window deserves some consideration, since it affects the calculation of SI. Previous studies mostly used one baseline reference window for each subject.[17,18] One study used reference windows that were updated each hour.[34] In our analysis, selection of a new reference window in the interictal phase for seizures occurring at least 90 minutes apart generated fewer false alarms. This indicates that baseline neural dynamics may change between seizures, and periodic updates in reference window may be necessary. Furthermore, the application of DBS during closed-loop stimulation would also affect the neural dynamics. This issue will have to be carefully determined through future long-term recordings, with the application of closed-loop DBS.

Conclusions

As anterior nucleus DBS becomes an accepted treatment for medically refractory epilepsy, a closed-loop solution is on the horizon and the search for a seizure prediction biomarker becomes pertinent. We have shown that a nonlinear method, by calculating similarity, can potentially predict and detect seizures from thalamic DBS signals. These findings need to be validated in future prospective studies to assess efficacy of a closed-loop thalamic stimulation system.

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Disclosures

Dr. Lozano reports that he has ownership in Functional Neuromodulation and is a consultant for Medtronic, Boston Scientific, and St. Jude.

Author Contributions

Conception and design: Krishna, So, King, Wennberg. Acquisition of data: Krishna, King, Sammartino, Lozano, Wennberg. Analysis and interpretation of data: Krishna, So, King, Yang, Zhang, Guan. Drafting the article: Krishna, So, Sammartino. Critically revising the article: Krishna, King, Lozano, Wennberg, Guan. Reviewed submitted version of manuscript: King, Yang, Zhang, Sammartino, Wennberg, Guan. Approved the final version of the manuscript on behalf of all authors: Krishna. Statistical analysis: So. Study supervision: Lozano, Guan.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Table 1 and Fig. 1. https://thejns.org/doi/suppl/10.3171/2016.7.JNS161282.

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