

Electroencephalography Measures are Useful for Identifying Large Acute Ischemic Stroke in the Emergency Department

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Background: Early diagnosis of stroke optimizes reperfusion therapies, but behavioral measures have incomplete accuracy. Electroencephalogram (EEG) has high sensitivity for immediately detecting brain ischemia. This pilot study aimed to evaluate feasibility and utility of EEG for identifying patients with a large acute ischemic stroke during Emergency Department (ED) evaluation, as these data might be useful in the prehospital setting. *Methods:* A 3-minute resting EEG was recorded using a dense-array (256-lead) system in patients with suspected acute stroke arriving at the ED of a US Comprehensive Stroke Center. *Results:* An EEG was recorded in 24 subjects, 14 with acute cerebral ischemia (including 5 with large acute ischemic stroke) and 10 without acute cerebral ischemia. Median time from stroke onset to EEG was 6.6 hours; and from ED arrival to EEG, 1.9 hours. Delta band power ($P = .004$) and the alpha/delta frequency band ratio ($P = .0006$) each significantly distinguished patients with large acute ischemic stroke ($n = 5$) from all other patients with suspected stroke ($n = 19$), with the best diagnostic utility coming from contralesional hemisphere signals. Larger infarct volume correlated with higher EEG power in the alpha/delta frequency band ratio within both the ipsilesional ($r = -0.64$, $P = .013$) and the contralesional ($r = -0.78$, $P = .001$) hemispheres. *Conclusions:* Within hours of stroke onset, EEG measures (1) identify patients with large acute ischemic stroke and (2) correlate with infarct volume. These results suggest that EEG measures of brain function may be useful to improve diagnosis of large acute ischemic stroke in the ED, findings that might be useful to pre-hospital applications.

Key Words: Acute stroke—electroencephalography—diagnosis—emergency medicine

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Introduction

Increasing data support the utility of endovascular therapy (EVT) for many patients with acute ischemic stroke. Early and accurate prescription of such reperfusion therapies would be facilitated by improved methods for rapidly identifying the target population, that is, patients with a large vessel occlusion appropriate for EVT, particularly in the prehospital setting.

Hill et al¹ divided the time window prior to EVT into 2 epochs, the first being stroke-onset-to-imaging time. This approach emphasizes that minutes saved getting the appropriate patients to the head scanner expeditiously are just as important as minutes saved between scanning and initiating reperfusion therapy: “911-to-door” times are just as important as “door-to-needle” times. Electroencephalogram (EEG) has long been known to have high sensitivity for immediate detection of brain ischemia² but currently has a limited role in acute stroke evaluation. Recent advances in EEG acquisition hardware, lead technology, and analysis software³ suggest a larger diagnostic role may be possible for patients with suspect acute stroke.

Clinical diagnosis of acute stroke by paramedics^{4,5} and by Emergency Department (ED) physicians^{6,7} is frequently inaccurate. Efforts are ongoing to improve clinical diagnostic methods.^{8,9} Electrophysiological assessment in the acute stroke setting may provide additional diagnostic information that complements what is learned from the behavioral exam. The long-term goal of these studies is to evaluate the utility of EEG in the prehospital setting to identify patients with a large acute ischemic stroke. Earlier identification of large acute ischemic strokes would allow for more accurate triage in the field and thus optimize decisions related to transport destination, facilitate earlier notification of stroke teams, and faster initiation of diagnostic evaluation and acute reperfusion therapies, all of which is intended to increase salvaged brain tissue and improve patient outcomes. As an initial step toward this goal, the current pilot study examined the feasibility of acquiring a 3-minute EEG recording in the ED and its diagnostic performance, hypothesizing that EEG-based measures have substantial diagnostic information in the acute stroke setting. This hypothesis was specifically tested by examining whether EEG measures of brain injury (1) correlate with infarct volume and (2) identify patients with large acute ischemic stroke.

Materials and Methods

Study Design

Patients with suspected acute ischemic stroke were recruited from the ED of the University of California Irvine Medical Center, a certified Comprehensive Stroke Center.^{10,11} Study personnel were notified by pager of patients with suspected acute stroke. Entry criteria were

suspected acute stroke, age 18 years or older, head computed tomography negative for hemorrhage, English-speaking, and no contraindication to EEG. The University of California Irvine Institutional Review Board approved this study. Patients or their surrogate gave informed consent. ED physicians approved enrollment and timing of each patient's procedures in order to prevent interruptions in care delivery. Final diagnosis was based on neuroimaging and discharge summary.

EEG Acquisition

Scalp EEG was recorded at the bedside for 3-minutes using a dense array (256-electrode) Hydrocel net (Electrical Geodesics Inc., Eugene, OR) as described previously.³ At no time did EEG delay initial brain imaging or administration of therapy in the ED. Patients were only enrolled into this study when the ED attending (1) completed initial assessment and (2) approved the patient for study enrollment.

The EEG signal was referenced to Cz during recording. During subsequent offline analyses, each lead's signal was rereferenced to the average across all leads within the same hemisphere. Leads were averaged to one hemisphere's leads, rather than all leads, in order to avoid one hemisphere's signals influencing values in the other hemisphere's results, that is, a contralesional lead was rereferenced to contralesional hemisphere leads only, and an ipsilesional lead was rereferenced to ipsilesional hemisphere leads only. EEG was recorded with no bandpass filter. Impedances were kept below 100 k Ω at all electrodes for all recordings. Data were recorded at 1000 Hz using a high input impedance Net Amp 300 amplifier and Net Station 4.5.3 software (Electrical Geodesics Inc., Eugene OR). Awake, resting-state EEG was recorded for 3 minutes. During recording, participants were positioned with head of bed at approximately 30° and were instructed to direct their gaze, as possible, toward the center of a fixation cross displayed at end of their gurney. To limit artifacts in the EEG signal from muscle activity, patients were instructed to minimize all movements during EEG recording.

EEG Processing

EEG data were exported to MATLAB 2015a 7.8.0 (MathWorks, Inc., Natick, MA) for offline analyses as described previously.³ To minimize muscle artifacts from electrodes overlying the neck and cheeks, 62 electrodes overlying these regions were excluded from analyses. The EEG recording then underwent a sixth-order, 50 Hz low-pass filter, was divided into consecutive nonoverlapping 1-second epochs, and was mean detrended. Epochs were visually inspected for contamination by overt muscle activity and removed from further analysis. EEG data then underwent an Independent Component Analysis-based artifact removal approach^{12,13} employed previously

by our group.^{3,14-16} For each resultant component, the time series, topographic distribution of signal amplitudes, frequency spectra, and frequency loading were used to identify and remove stereotypical artifacts. Components that only occurred in 1 channel were also removed. The remaining components were reconstituted in the time domain using the mixing matrix. Spectral analysis was performed by applying a discrete fast fourier transform (MathWorks, Inc., Natick, MA) to the 1-second epochs to obtain a frequency resolution of 1 Hz.

Spectral power was then extracted from EEG recordings. Two bands of particular interest were delta (measured in the 1-3 Hz band) and low beta (measured in the 13-19 Hz band) given their established relationship to clinical status during the acute stroke period.³ In addition, 2 validated quantitative EEG metrics of interest were ADR (ratio of 2 spectral power measures: alpha/delta, where alpha was measured in the 8-12 Hz band)¹⁷ and DTABR (ratio of 4 spectral power measures: (delta*theta)/(alpha*beta), where theta was measured in the 4-7 Hz band).¹⁸ The mean value for each was extracted from electrodes overlying whole brain, overlying the ipsilesional hemisphere, and overlying the contralesional hemisphere. EEG results were then again examined after rereferencing using a Laplacian transform.

Infarct Volume

Infarct volume was measured on the first magnetic resonance imaging or computed tomography scan that demonstrated the index stroke. These scans were acquired as part of standard of care. Infarcts were outlined using techniques for which reliability has been described previously.¹⁹

Statistical Analysis

Analyses used JMP 13.1 (SAS Institute Inc., Cary, NC) and were 2-tailed with significance defined using alpha <0.05. Spearman's rank-order correlation was used to examine the relationship between EEG measures and infarct volume (primarily) as well as with NIHSS score (secondarily). This was repeated, exploring the effect of a Laplacian transform. As the normality assumption was often not present, nonparametric methods were employed, with Bonferroni correction ($P = .0167$ to correct for 3 comparisons within each EEG measure). Nominal logistic regression modeling was used to determine the significance and odds ratio for the relationship between each EEG measure and diagnosis (large acute ischemic stroke versus other diagnosis).

Results

Patient Characteristics

Of 25 subjects recruited, EEG was recorded in 24, with acquisition halted in 1 subject due to vomiting. Mean (\pm SD) age was 64.8 ± 15.5 years, and the gender

distribution was 13 M/11 F. Of the 24 subjects, 14 (58%) had acute cerebral ischemia, 11 with radiologically confirmed acute ischemic stroke and 3 with TIA (Fig 1). For the 11 subjects with acute stroke, median infarct volume was 18.9 cc (interquartile range 1.5-44.5, range 0.5-105 cc), and median NIHSS score was 4 (interquartile range 3-6, range 0-19). Ten subjects were initially suspected of having acute stroke but ultimately discharged with a nonstroke diagnosis: seizure ($n = 2$), metabolic encephalopathy ($n = 2$), panic attack ($n = 2$), or hypertensive encephalopathy ($n = 4$).

Table 1 summarizes the timeline for EEG acquisition. Median time from stroke onset to EEG was 6.6 hours; and from ED arrival to EEG, 1.9 hours. Median time from consent to start of EEG was 11 minutes and was as short as 5 minutes. The median time from EEG to neuroimaging among patients with stroke (the first images that showed the index infarct, and so were used to measure infarct volume) was 3.8 hours. Four patients received IV tissue plasminogen activator, 3 prior (median 61 minutes) to EEG and 1 after (28 minutes) EEG. No patient was treated with endovascular therapy.

EEG in the ED Correlated with Final Infarct Volume

Among patients with acute cerebral ischemia, infarct volume correlated with several EEG measures, particularly ADR (Table 2, Fig 2). Values in both the ipsilesional hemisphere and the contralesional hemisphere were related to infarct volume. Results were overall robust, for example, if instead examining alternative EEG metrics (DTABR), if only looking at the 20 electrodes present in a 10-20 EEG lead montage (rather than all 256 leads), or if correlating EEG with NIHSS score rather than infarct volume.

EEG to Identify Large Acute Ischemic Infarcts

The performance of EEG for distinguishing patients with a large acute ischemic infarct from patients lacking a large acute ischemic infarct was examined. Imposing a conservative threshold of 20 cc infarct volume²⁰ identified 5 patients with a large acute ischemic stroke, all of whom had injury restricted to supratentorial territories. Many EEG measures distinguished these 5 patients with large acute ischemic stroke from the other 19 patients (Table 3). Results were again robust if examining only the 20 electrodes present in a 10-20 EEG lead montage rather than all 256 leads. Note that no EEG measure significantly distinguished "any acute cerebral ischemia" ($n = 14$) from nonischemia ($n = 10$).

Electrophysiological Changes During Ischemic Stroke are Diffuse

Using the Laplacian transform, no EEG measure correlated with infarct volume or with NIHSS score ($P > .1$).

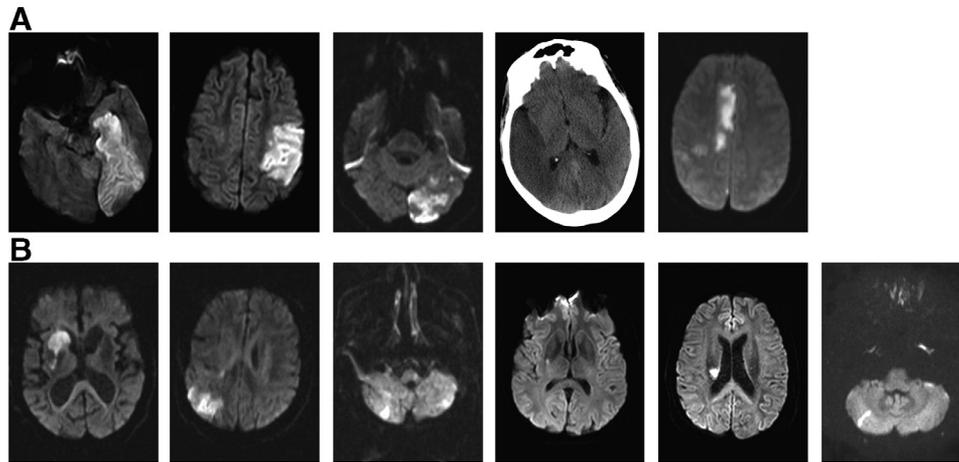


Figure 1. Diagnostic brain imaging in the 11 patients diagnosed with acute ischemic stroke. (A) Images of the 5 patients with infarct volume >20 cc. (B) Images of the six patients with stroke volume ≤20 cc.

Table 1. Timeline in relation to ED presentation and EEG acquisition

	All patients	Patients with acute cerebral ischemia	Nonischemia patients
n	24	14	10
Symptom onset-ED arrival (hours)	4.2 (1.5-15.5)	3.4 (1.3-9.5)	6.6 (3.1-37.2)
Symptom onset-EEG (hours)	6.6 (3.9-31.1)	5.8 (3.4-26.4)	9.3 (4.2-43.5)
ED arrival-EEG (hours)	1.9 (1.1-3.0)	1.7 (1.0-2.8)	1.9 (1.1-3.3)
Consent-EEG (minutes)*	11 (7.5-17.5)	11 (7.5-11.5)	13.5 (6.5-20.5)

Values are median (IQR).

*Data available from final 13 subjects.

Table 2. EEG correlates in patients with acute cerebral ischemia

EEG measure	256 lead				20 leads			
	Correlation with infarct volume		Correlation with NIHSS score		Correlation with infarct volume		Correlation with NIHSS score	
	r	P	r	P	r	P	r	P
Delta (1-3 Hz) power								
Whole brain	.63	.016*	.53	.05*	.70	.005 [†]	.56	.037*
Ipsilesional hemisphere	.55	.04*	.46	.099	.48	.08	.30	.29
Contralesional hemisphere	.60	.02*	.52	.057	.62	.018*	.57	.03*
Beta (13-19 Hz) power								
Whole brain	-.56	.038*	-.53	.049*	-.57	.03*	-.52	.055
Ipsilesional hemisphere	-.49	.08	-.34	.24	-.42	.13	-.40	.16
Contralesional hemisphere	-.56	.036*	-.49	.07	-.63	.0158*	-.57	.02*
ADR								
Whole brain	-.70	.0058 [‡]	-.64	.013*	-.75	.002 [†]	-.68	.008 [†]
Ipsilesional hemisphere	-.64	.013*	-.61	.02*	-.69	.006 [†]	-.67	.009 [†]
Contralesional hemisphere	-.78	.001 [‡]	-.75	.002 [†]	-.68	.008 [†]	-.68	.008 [†]
DTABR								
Whole brain	.54	.046*	.56	.036*	.70	.005 [†]	.70	.005 [†]
Ipsilesional hemisphere	.49	.08	.46	.097	.59	.025*	.61	.02*
Contralesional hemisphere	.66	.01 [†]	.65	.01 [†]	.70	.0058 [‡]	.73	.003 [†]

DTABR = (delta*theta)/(alpha*beta); ADR = alpha/delta; The 20 leads represent analysis restricted to the standard leads from a 10-20 EEG electrode montage.

*P ≤ .05.

[†]P ≤ .01.

[‡]P ≤ .001.

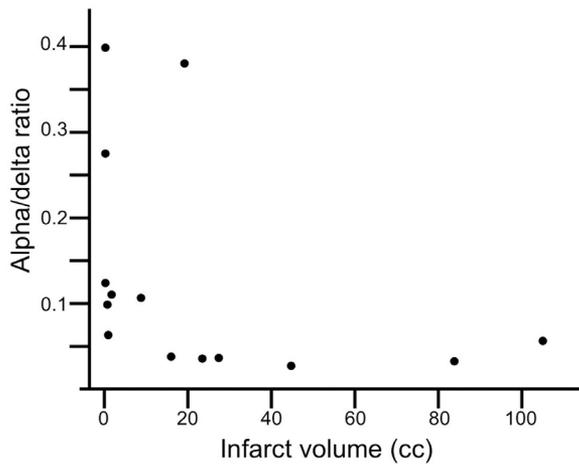


Figure 2. EEG measures correlate with infarct volume in patients with acute cerebral ischemia. ADR (ratio of alpha power to delta power) for whole brain (all 20 leads) in a 10-20 montage is plotted in relation to infarct volume ($r = -.75$, $P = .002$, Spearman's rho).

Discussion

EEG was obtained in 24 subjects with suspected stroke in the ED. Among patients with acute cerebral ischemia, infarct volume had a robust, linear relationship with several EEG measures (Table 2). EEG helps identify patients with large acute infarct volumes (Table 3). EEG measures in this pilot study contained information useful for distinguishing large acute ischemic strokes from other patients suspected of acute stroke, suggesting that EEG could potentially be useful in the prehospital setting to improve diagnosis of patients with large acute ischemic

strokes and thus potentially those patients with large vessel occlusion.

Findings in the current pilot study support the feasibility and validity of EEG for identifying large ischemic strokes in the ED. EEG measures have long been known to vary with the severity and volume of cerebral ischemia.²¹ However, while there have been prior presentations of EEG data collection from patients with acute stroke in an ED setting,²¹ this is the first report of patients assessed during the acute stroke workflow in the ED of a Comprehensive Stroke Center. To date, the cohort studied at the earliest time poststroke obtained EEG an average of 6.6 hours poststroke,²² however that study focused on correlates of EEG change over 1 week, an approach less informative with respect to acute stroke diagnosis. While current findings support the utility of EEG for diagnosing large acute ischemic strokes, EEG data did not perform well at identifying any acute cerebral ischemia, but given the heterogeneity of acute ischemic infarcts, it is not surprising that a diagnostic test for acute ischemic stroke of any size is less accurate than a test for a large acute ischemic stroke.

Infarct volume correlated best with ADR, perhaps because this EEG measure captures both the increased power in low (delta) frequencies and the decreased power in high (alpha) frequencies that arise as a result of an acute stroke. EEG correlated with infarct volume more strongly than with NIHSS score (Table 2) likely because EEG more closely reflects injury than it does an ordinal measure of global behavioral deficits.

Findings in the contralesional hemisphere showed a remarkably strong relationship with infarct volume and with acute large ischemic stroke status (Tables 2 and 3).

Table 3. EEG measures distinguishing large acute ischemic stroke from other diagnoses

EEG measure	256 leads		20 leads	
	P	OR (95% CI)	P	OR (95% CI)
<i>Delta (1-3 Hz) power</i>				
Whole brain	.008 [†]	.88 (0.78-0.99)	.0005 [‡]	.47 (0.24-0.91)
Ipsilesional hemisphere	.038*	.91 (0.83-1.0)	.028*	.73 (0.53-1.0)
Contralesional hemisphere	.004 [†]	.87 (0.77-0.99)	.0008 [‡]	.57 (0.33-0.98)
<i>Beta (13-19 Hz) power</i>				
Whole brain	.07	1.3 (0.94-1.75)	.09	2.1 (0.79-5.55)
Ipsilesional hemisphere	.18	1.2 (0.89-1.6)	.30	1.45 (0.69-3.1)
Contralesional hemisphere	.04*	1.27 (0.97-1.66)	.036*	2.7 (0.86-8.6)
<i>ADR</i>				
Whole brain	.001 [‡]	22,695 (0.28-1.9e+9)	.0008 [‡]	8.8e+28 (0.0002-4.8e+61)
Ipsilesional hemisphere	.005 [†]	686 (0.42-1,128,398)	.004 [†]	7.6e+19 (0.18-3.3e+40)
Contralesional hemisphere	.0006 [‡]	138,135 (0.52-3.6e+10)	.0004 [‡]	5.2e+38 (7.1e-12-3.8e+88)
<i>DTABR</i>				
Whole brain	.03*	1.8e-5 (2.4e-10-1.36)	.012*	.56 (0.33-0.96)
Ipsilesional hemisphere	.11	0.0004 (1.7e-8-9.9)	.06	.67 (0.43-1.05)
Contralesional hemisphere	.015*	1.0e-5 (1.8e-10-0.59)	.003 [†]	.48 (0.24-0.94)

OR = odds ratio; odds of “no” versus “yes” per unit change in regressor.

* $P < .05$

[†] $P < .01$

[‡] $P < .001$.

Confidence that these clinical associations with contralateral EEG findings are not due to contamination by ipsilateral hemisphere signals is increased based on the rereferencing approach used herein (a given lead was rereferenced only to other leads within the same hemisphere), an approach facilitated by dense array EEG data collection. Bilateral EEG changes are a well-established finding early after unilateral stroke.^{3,23-33} However, contralateral changes generally have not overshadowed those found ipsilaterally. The reason for the current finding of contralateral predominance in this cohort is unclear and may reflect the very early time points poststroke when recordings were obtained, use of dense array EEG, features of the patient population studied, method of rereferencing, or other factors. The biological significance of this finding might reflect very early changes in interhemispheric connectivity.^{30,33} Bilateral changes are also seen with conditions affecting the brain globally, such as encephalopathy, and while EEG distinguished such cases from stroke in the current pilot study, larger studies are needed to interpret such findings with confidence.

The same EEG measures that correlated with infarct volume and NIHSS did not show a significant correlation with these 2 measures when the Laplacian transform was applied, indicating that EEG changes after stroke are diffuse. The Laplacian transform is a second spatial derivative along the scalp. While sensitive to highly focal voltage changes, the Laplacian transform misses diffuse broad voltage changes, and so misses the broadly distributed EEG changes that have been reported in the acute setting—EEG findings on a larger spatial scale are spatially filtered out by use of surface Laplacian estimates.^{34,35}

Limitations of the current pilot study include a modest sample size, enrollment of mainly mild-moderate stroke, and a focus on only ischemic stroke (which resulted in no data on intracerebral hemorrhage). Consent was delayed after ED arrival (although 25% of patients had EEG performed <3.4 hours after stroke onset), as the EEG was recorded only after an ED physician gave approval—this study was focused on feasibility not speed of EEG recording in the ED. Artifact detection and data analysis were performed offline but would need to be streamlined and automated for any prehospital EEG applications. Also, this was a proof-of-concept pilot study that used dense-array EEG to probe with maximum sensitivity the utility that EEG has in the ED evaluation of suspected acute stroke. Moving forward, further study of EEG as a potential tool for very early diagnosis of large ischemic strokes should consider use of EEG hardware that is more appropriate for rapid implementation in the prehospital setting. A 256-electrode net was chosen for this feasibility study in order to record high-resolution data, employing a system that also allows for rapid application. This permitted comparison with low-resolution data (10-20 montage, obtained by reducing data dimensionality); [Tables 2 and 3](#) suggest that indeed 20 leads have the same diagnostic utility as the 256-

lead net. In this regard, findings in the current study using a 10-20 lead simulation ([Tables 2 and 3](#)) suggest the utility of an approach with alternate EEG hardware, such as a dry lead system, or possibly an EEG net that has fewer leads and can be applied more rapidly in the field. Other potential applications of EEG in the context of suspected acute ischemic stroke, beyond prehospital diagnosis, might include improved monitoring, for example, for recanalization, PH2 hemorrhagic transformation, malignant edema, or epileptiform activity, although these were not in the scope of the current study.

Paramedics^{4,5} and ED physicians^{6,7} are frequently inaccurate in their clinical diagnosis of acute stroke. Improved methods to accurately identify acute stroke, and thus EVT candidates, are needed, as these could shorten 911-to-door times and potentially increase rates of EVT administration. EEG provides useful information about whether a large acute ischemic stroke is present ([Table 3](#)) and might ultimately contribute to prehospital on-scene diagnosis of acute stroke. The approach could theoretically emulate how electrocardiogram informs evaluation of acute chest pain, whereby paramedics place leads quickly, continue their evaluation, then review computerized interpretation of electrophysiological results, minimally affecting on-scene time. Improved diagnosis of strokes, particularly large acute ischemic strokes, in the prehospital setting would inform triage, transport destination decisions, and ultimately foster greater salvage of acutely threatened brain tissue to improve patient outcomes.

EEG recordings provide useful diagnostic information in the evaluation of patients with suspected stroke. This study supports the feasibility of acquiring EEG recordings during the ED acute stroke workflow of a busy Comprehensive Stroke Center and characterizes the electrophysiological changes seen in patients with large acute ischemic stroke. Specific EEG metrics were found to identify patients with large acute ischemic stroke and to correlate with infarct volume. Recent advancements in EEG technology have made EEG increasingly portable and easier to use, supporting the potential utility of this approach to improving stroke diagnostics. Long-term studies extending from the current pilot study might examine the utility of EEG to inform the diagnosis of stroke in the prehospital setting, shortening 911-to-door times and increasing rates of EVT.

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Conflicts of Interest

Dr. Cramer serves as a consultant for Abbvie, Constant Therapeutics, MicroTransponder, Neuroolutions, Regenera, SanBio, Stemedica, Biogen, Fujifilm Toyama Chemical, and TRCare.

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