UCLA
UCLA Previously Published Works

Title

A Measure of Neural Function Provides Unique Insights into Behavioral Deficits in Acute Stroke.

Permalink

https://escholarship.org/uc/item/7sz393x0

Journal

Stroke, 54(2)

Authors

Vanderschelden, Benjamin
Erani, Fareshte
Wu, Jennifer
et al.

Publication Date

2023-02-01

DOI

10.1161/STROKEAHA.122.040841

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Stroke. 2023 February ; 54(2): e25–e29. doi:10.1161/STROKEAHA.122.040841.

A measure of neural function provides unique insights into behavioral deficits in acute stroke

Benjamin Vanderschelden, MD[1], **Fareshte Erani, MS**[1], **Jennifer Wu, MD, PhD**[2], **Adam de Havenon, MD**[3], **Ramesh Srinivasan, PhD**[4], **Steven C. Cramer, MD**[1,5]

[1]Dept. Neurology, University of California, Irvine

[2]Dept. Pediatric Rehabilitation Medicine, Spaulding Rehabilitation Hospital and Harvard Medical School; Boston, MA

[3]Dept. Neurology, Yale University

[4]Dept. Cognitive Science, University of California, Irvine

[5]Dept. Neurology, UCLA; California Rehabilitation Institute, Los Angeles

Abstract

Background: Clinical and neuroimaging measures incompletely explain behavioral deficits in the acute stroke setting. We hypothesized that EEG-based measures of neural function would significantly improve prediction of acute stroke deficits.

Methods: Patients with acute stroke (n=50) seen in the Emergency Department of a university hospital from 2017–2018 underwent standard evaluation followed by a 3-minute recording of EEG at rest using a wireless, 17-electrode, dry-lead system. Artifacts in EEG recordings were removed offline then spectral power was calculated for each lead pair. A primary EEG metric was DTABR, calculated as a ratio of spectral power: [(Delta*Theta)/(Alpha*Beta)]. Bivariate analyses and LASSO regression identified clinical and neuroimaging measures that best predicted initial NIHSS score. Multivariable linear regression was then performed before vs. after adding EEG findings to these measures, using initial NIHSS score as the dependent measure.

Results: Age, diabetes status, and infarct volume were the best predictors of initial NIHSS score in bivariate analyses, confirmed using LASSO regression. Combined in a multivariate model, these three explained initial NIHSS score (adjusted r^2=0.47). Adding any of several different

Corresponding Author: Steven C. Cramer, Dept. Neurology, UCLA, California Rehabilitation Institute, 2070 Century Park East, Los Angeles, CA 90067-1907, (424) 522-7273, sccramer@mednet.ucla.edu.
Department Social Medial Handle: @UCLANeurology (Twitter)

Disclosures

Dr. Cramer consulted for Abbvie, Constant Therapeutics, SanBio, Panaxium, NeuExcell, Elevian, Helius, Omniscient, Brainsgate, MicroTransponder, Neurolutions, Medtronics, and TRCare; and receives support from NIH. Dr. de Havenon received investigator-initiated funding from AAN, Regeneron, AMGEN, and AMAG pharmaceuticals; royalty fees from UpToDate; consulted for Integra and Novo Nordisk; has equity in TitinKM and Certus; and receives support from NIH.

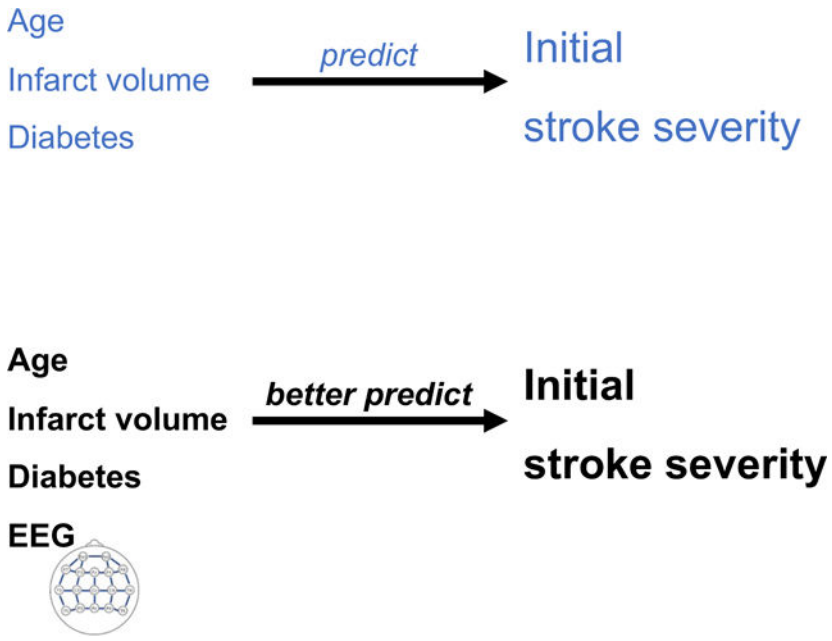
Supplemental Material
Supplemental Methods
Supplemental Results
Tables S1–S4
Two references[10,11]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

EEG measures to this clinical model significantly improved prediction; the greatest amount of additional variance was explained by adding contralesional DTABR (adjusted r^2= 0.60, p<0.001).

Conclusion: EEG measures of neural function significantly add to clinical and neuroimaging for explaining initial NIHSS score in the acute stroke Emergency Department setting. A dry-lead EEG system can be rapidly and easily implemented. EEG contains information that may be useful early after stroke.

Graphical Abstract



Introduction

Understanding the pathophysiology of acute stroke informs clinical decision-making. Measures of infarct volume incompletely explain acute behavioral deficits[1,2] and are usually unavailable in some settings, e.g., prehospital evaluation. We previously reported that high-dimension EEG data recorded during the initial days after stroke onset are strongly correlated with acute stroke behavioral deficits[3]. The current study aimed to determine whether EEG measures are related to acute deficits in the initial hours post-stroke using a dry-lead EEG system that is rapidly[4] applied to the scalp. We examined the extent to which clinical and neuroimaging measures predict initial NIHSS score, hypothesizing that adding EEG measures would significantly improve this prediction.

Methods

Patients:

Patients were recruited as part of a larger study investigating the ability of EEG to distinguish acute stroke from non-stroke[4]. In that study, patients presenting to the ED at the UC Irvine Medical Center with suspected or definite stroke were offered enrollment (1/30/2017–7/1/2018); 100 patients with suspected stroke were enrolled, 50 with acute

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

stroke and 50 with stroke mimics. The current report is focused on the 50 patients with a final diagnosis of acute stroke. Final diagnosis was based on discharge summary. Patients or surrogates provided informed consent as approved by the IRB. This study is reported in compliance with STROBE guidelines. Data will be shared with other investigators as possible.

EEG acquisition:

The Quick-20 (Cognionics, Inc., San Diego, CA, USA) EEG system uses dry-contact electrodes and is supported by a local active amplifier plus Faraday cage. The current system used a 17-lead array (Figure 1A), with reference and ground electrodes adjacent to Fp1 and Fp2, respectively. Three minutes of eyes-open, resting-state brain activity were recorded at the bedside.

EEG pre-processing:

EEG data were exported to MATLAB 2015a 7.8.0 for offline analysis. A second-order 50 Hz low-pass Butterworth filter and 0.2 Hz high-pass Butterworth filters were applied. Visual inspection was used to identify then remove channels and one-second epochs containing artifact.

EEG analysis:

Power in each lead pair (Figure 1A) was calculated in delta (1–3 Hz), theta (4–6 Hz), alpha (7–12 Hz), and beta (13–30 Hz) bands. DTABR [(Delta*Theta)/(Alpha*Beta)] was calculated. Ipsilesional leads were designated as odd numbers. Based on prior EEG studies in acute stroke from our group[3,5], primary analysis focused was on increased delta power, decreased beta power, and increased DTABR.

Infarct volume:

Infarct volume was measured on the first MRI or CT scan that demonstrated the index stroke, ordered as standard of care.

Clinical variables:

Clinical and demographic data were extracted from the medical record.

Statistical analyses:

Parametric statistical methods were used, as measures were either normally distributed or could be transformed to be so. Bivariate analyses screened each of eight clinical and radiological measures (Table 1) as a predictor of initial NIHSS score using linear regression models; in this screening step, a threshold of $p<0.1$ was used, akin to the approach used in the screening stage of stepwise modeling. As a secondary approach, the same eight clinical and radiological measures were entered into a LASSO model[6], run with 10-fold cross-validation and 100 lambdas.

A baseline multivariable linear regression model was run with initial NIHSS score as the dependent measure and predictors with a bivariate $p<0.1$, identified in the above screening

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

stage, as independent measures. To determine the amount of variance in initial NIHSS score that was explained by the baseline model, adjusted r^2 was calculated, which appropriately penalizes the addition of variables. To understand if the EEG measures improved predictive value, we individually added them to the baseline model and compared the resulting adjusted r^2value to that of the baseline multivariable model using the likelihood ratio test. Bonferroni correction accounted for use of nine (Table 2) analyses and thus set significance at p=0.006. The BIC for each model is also reported. All models were checked for multicollinearity by establishing that the variance inflation factor was <5 for individual covariates. The link test was used to determine if the model was specified correctly. Marginal effects were used in multivariable regression models to show the predicted initial NIHSS score by the EEG exposure with the highest adjusted r^2 value while holding covariates constant.

Results

Subject Characteristics:

The 50 subjects (Table S1) had age 65.6±17.7 years (mean ± SD), with 40% female. A total of 82% were White, 14% Asian, and 4% African American. Ethnicity was Hispanic in 26%. There were 43 subjects with ischemic stroke and 7 with intracerebral hemorrhage. Infarcts were on the right in 54% and had mean volume of 24.5±44.4 cc. Median [IQR] initial NIHSS score was 4 [1–8]; NIHSS subscores appear in Table S2. Time from last known well to EEG was 10.6 hours [5.4–16.5]. There were no missing data. Across the 50 EEG recordings, 76±35.3 (mean±SD) of the 180 epochs per EEG exam were retained for subsequent analysis after visual inspection.

Bivariate Correlations and LASSO regression:

To define the best clinical predictor model, each clinical and radiological measure was examined with respect to initial NIHSS score. Three measures met the threshold ($p<0.1$): age, diabetes status, and infarct volume (Table 1, “Bivariate analysis”). LASSO regression identified the same three measures as the most important predictors.

Linear regression:

The baseline multivariate clinical model using age, diabetes status, and infarct volume as predictors had adjusted $r^2=0.47$, indicating that 47% of the variance in initial NIHSS score was explained by these three measures. Adding EEG measures to this clinical model significantly improved prediction, indicated by a lower BIC and higher adjusted r^2 (Table 2). Compared to other primary (Table 2) and secondary (Table S3) EEG variables, the greatest amount of additional variance was explained by adding contralesional DTABR (adjusted $r^2= 0.60$, $p<0.001$). For each measure in Table 2, adding contralesional EEG data improved NIHSS score prediction more than adding ipsilesional or whole brain values for that EEG metric. Findings among only patients with ischemic stroke (n=43) were largely concordant (Table S4).

The relationship between the initial NIHSS score and contralesional DTABR appears in Figure 1B. In Figure 1C, the predicted initial NIHSS score is seen in relation to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

contralesional DTABR after adjusting for age, diabetes, and infarct volume, highlighting that an EEG measure (contralesional DTABR) has predictive ability even after adjusting for the clinical/radiological measures that predict NIHSS score.

Discussion

The relationship between acute stroke injury and behavioral deficits is incompletely understood[1,2], as extent of cerebral injury does not completely explain inter-subject differences in acute stroke deficits. We hypothesized that EEG-based measures of neural function provide further insights. Current findings, rapidly acquired using a 17-lead dry-lead EEG system, support this hypothesis, as EEG measures of brain function significantly added to demographics and infarct volume for explaining initial NIHSS score in acute stroke patients in the Emergency Department.

Convergent evidence suggests that the best clinical and radiological predictive measures were identified for the clinical model, as the three measures identified in bivariate correlations (age, diabetes status, and infarct volume) were independently confirmed using LASSO regression; together these comprised the baseline clinical model, which explained 47% of the variance in initial NIHSS score. Several EEG measures when added to this baseline clinical model significantly improved prediction, showing higher adjusted r^2 and lower BIC values, the most powerful of which was contralesional DTABR which when added to the model explained 60% of the variance. DTABR has previously been reported to be the strongest EEG predictor of functional outcome[7]. Together these findings suggest that an EEG measure such as contralesional DTABR provides unique and significant information about acute stroke deficits, beyond what can be learned from clinical and radiological measures; in the future, acute stroke care might include an EEG assessment to capture this information and thereby improve clinical decision making.

Bilateral EEG changes early after unilateral stroke have been described for decades and may reflect the immediate, widespread, and lasting changes in cortical inhibition that are seen bilaterally after unilateral stroke[8]. Contralesional changes are the strongest EEG measures that correlate with infarct volume in the acute stroke setting[5] and are not attributable to mass effect[3], indicating that EEG captures significant information about acute stroke effects not available from MRI. The reasons for contralateral predominance for explaining initial NIHSS score is unclear but may include reduced ipsilesional signal-to-noise due to substantial diaschisis in the region of the infarct, or disruption of interhemispheric projections from the ipsilesional to contralesional hemisphere; note that the predictive strength of ipsilesional EEG changes was also substantial.

Limitations of this study include a modest sample size, overall mild-moderate stroke severity among enrollees, and enrollment of mainly White patients. As such, the current cohort may not be fully representative of the overall population of patients with stroke.

Electrical changes have long been known to be sensitive to injury effects, even prior to cerebral infarction[9]. Current findings suggest that EEG may be useful to understand the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

pathophysiology of acute stroke effects on the brain and may contain data useful to clinical decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources

Supported by grants UL1 TR001414 and K23NS105924 from the NIH as well as the American Academy of Neurology Medical Student Research Scholarship. We thank Cognionics, Inc. for providing EEG components.

Abbreviations:

DTABR	(Delta*Theta)/(Alpha*Beta)

References

1. Helenius J, Henninger N. Leukoaraiosis Burden Significantly Modulates the Association Between Infarct Volume and National Institutes of Health Stroke Scale in Ischemic Stroke. Stroke. 2015;46:1857–1863. doi: 10.1161/STROKEAHA.115.009258 [PubMed: 25999386]
2. Saver J, Johnston K, Homer D, Wityk R, Koroshetz W, Truskowski L, Haley E. Infarct volume as a surrogate or auxiliary outcome measure in ischemic stroke clinical trials. The RANTTAS Investigators. Stroke. 1999;30:293–298. [PubMed: 9933262]
3. Wu J, Srinivasan R, Burke Quinlan E, Solodkin A, Small SL, Cramer SC. Utility of EEG measures of brain function in patients with acute stroke. J Neurophysiol. 2016;115:2399–2405. doi: 10.1152/jn.00978.2015 [PubMed: 26936984]
4. Erani F, Zolotova N, Vanderschelden B, Khoshab N, Sarian H, Nazarzai L, Wu J, Chakravarthy B, Hoonpongsimanont W, Yu W, et al. Electroencephalography Might Improve Diagnosis of Acute Stroke and Large Vessel Occlusion. Stroke. 2020;51:3361–3365. doi: 10.1161/STROKEAHA.120.030150 [PubMed: 32942967]
5. Shreve L, Kaur A, Vo C, Wu J, Cassidy JM, Nguyen A, Zhou RJ, Tran TB, Yang DZ, Medizade AI, et al. Electroencephalography Measures are Useful for Identifying Large Acute Ischemic Stroke in the Emergency Department. J Stroke Cerebrovasc Dis. 2019;28:2280–2286. doi: 10.1016/j.jstrokecerebrovasdis.2019.05.019 [PubMed: 31174955]
6. Tibshirani R. Regression shrinkage and selection via the Lasso. Journal of the Royal Statistical Society, Series B. 1996;58:267–288.
7. Doerrfuss JI, Kilic T, Ahmadi M, Holtkamp M, Weber JE. Quantitative and Qualitative EEG as a Prediction Tool for Outcome and Complications in Acute Stroke Patients. Clin EEG Neurosci. 2020;51:121–129. doi: 10.1177/1550059419875916 [PubMed: 31533467]
8. Redecker C, Wang W, Fritschy J, Witte O. Widespread and long-lasting alterations in GABA(A)-receptor subtypes after focal cortical infarcts in rats: mediation by NMDA-dependent processes. J Cereb Blood Flow Metab. 2002;22:1463–1475. [PubMed: 12468891]
9. Astrup JS L; Branston NM; Lassen NA Cortical Evoked Potential and Extracellular K+ and H+ at Critical Levels of Brain Ischemia. Stroke. 1977;8:51–57. [PubMed: 13521]
10. van Putten MJ, Peters JM, Mulder SM, de Haas JA, Bruijninckx CM, Tavy DL. A brain symmetry index (BSI) for online EEG monitoring in carotid endarterectomy. Clinical neurophysiology. 2004;115:1189–1194. doi: 10.1016/j.clinph.2003.12.002 [PubMed: 15066544]
11. Marini F, Lee C, Wagner J, Makeig S, Gola M. A comparative evaluation of signal quality between a research-grade and a wireless dry-electrode mobile EEG system. J Neural Eng. 2019;16:054001. doi: 10.1088/1741-2552/ab21f2 [PubMed: 31096191]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

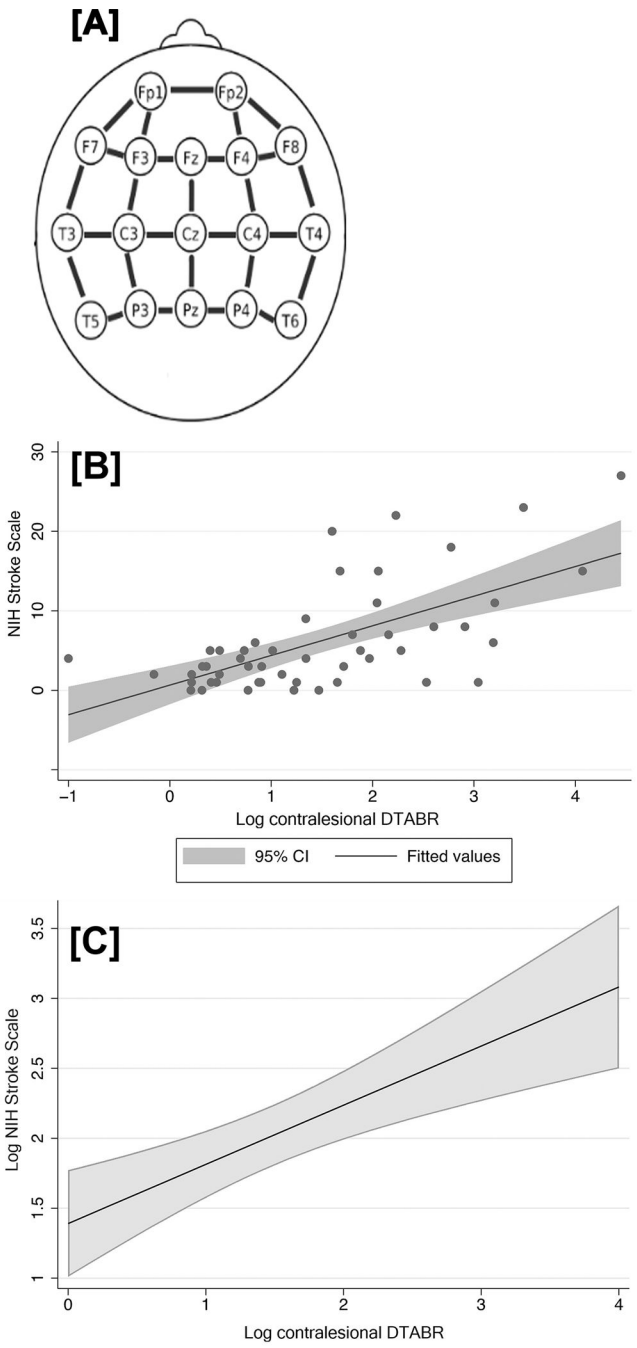


Figure 1.

[A] EEG recording montage. [B] Scatterplot with line of best fit and 95% CI of initial NIHSS score in relation to contralesional DTABR values. [C] Predicted NIHSS score from contralesional DTABR after adjusting for age, diabetes, and infarct volume.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Linear regression fit for predicting initial NIHSS score

Variable	Bivariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Age	0.02 (−0.002, 0.04)	0.078	0.01 (−0.005, 0.03)	0.177
Male sex	−0.36 (1.07, 0.34)	0.306		
Hypertension	0.14 (−0.67, 0.96)	0.728		
Hyperlipidemia	−0.17 (−0.87, 0.54)	0.634		
Diabetes	−0.83 (−1.64, −0.03)	0.043	−0.52 (−1.16, 0.12)	0.107
Right hemisphere	0.34 (−0.36, 1.03)	0.336		
Hours since last well	−0.01 (−0.08, 0.07)	0.887		
Infarct volume	0.88 (0.58, 1.17)	<0.001	0.84 (0.56, 1.12)	<0.001

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Effect of adding EEG variables to the baseline clinical model to predict initial NIHSsS score

Model	Adjusted r^2	BIC	p
Clinical model (age, diabetes, infarct volume)	0.47	141.0	
Clinical model + Whole brain delta	0.54	137.0	0.005
Clinical model + Ipsilesional delta	0.51	140.4	0.034
Clinical model + Contralesional delta	0.57	133.5	<0.001
Clinical model + Whole brain beta	0.56	134.0	0.001
Clinical model + Ipsilesional beta	0.53	137.9	0.008
Clinical model + Contralesional beta	0.59	130.6	<0.001
Clinical model + Whole brain DTABR	0.57	133.9	0.002
Clinical model + Ipsilesional DTABR	0.53	138.0	0.009
Clinical model + Contralesional DTABR	**0.60**	**129.7**	**<0.001**

Higher r^2 and lower BIC values indicate better model fit.