Evaluating the Clinical Impact of Rapid Response Electroencephalography: The DECIDE Multicenter Prospective Observational Clinical Study Does Use of Rapid Response EEG Impact Clinical Decision Making

Supplementary Online Content

SUPPLEMENTARY METHODS

eMethods 1: Study Protocol

To date, there is little systematic information regarding how physicians handle possible non-convulsive seizures when EEG is delayed or unavailable or how rapid access to EEG could affect physicians' diagnostic suspicions and treatment decisions. Moreover, to our knowledge no systematic study has addressed physicians' confidence in their own diagnosis and treatment plans when they face possible cases of non-convulsive seizures without access to EEG data.

The current study was designed to address this gap of knowledge. Physicians and patients were enrolled during both weekday business hours (Monday-Friday, 9am-5pm) and after-hours (nights and weekends) between April 2018 and April 2019; each site started and ended recruitment at different time points within the study period. Each participating physician completed a training session on the use of Rapid-EEG, which included watching videos describing its setup (20 minutes) and its Brain Stethoscope function (15 minutes) including a qualification test, as well as a hands-on session (45 minutes) that included a live demo of Rapid-EEG setup. Physicians completed a four-item questionnaire before applying the Rapid-EEG system which ascertained physicians' suspicion for seizure (yes or no), plan to escalate treatment with anti-seizure medications (yes or no), and confidence in their diagnostic assessment and therapeutic decision (rated on a 5-point Likert scale of 1="very low" to 5="very high"). The same bedside physicians then applied the Rapid-EEG system themselves (without the help of EEG technologists) and were instructed not to delay the conventional EEG system in the process of administering the Rapid-EEG system. After applying the Rapid-EEG system, physicians listened to sonified EEG (30 seconds from each hemisphere) using the Brain Stethoscope function (1) and then reviewed visual EEG (60 seconds) at the bedside using the Rapid-EEG device's visual display. Afterwards, physicians were asked to fill out the same four-item questionnaire given prior to Rapid-EEG set up, in addition to a questionnaire asking them to rate the ease of use of the headband and the recording device (both on a 5-point Likert scale of 1="difficult" to 5="easy"). After the device was removed, study coordinators detailed any device-related difficulties or any problems with the patient's scalp as a result of applying the device. The Rapid-EEG system would continue recording from the patient until the conventional EEG system arrived, at which time it was disconnected by the EEG technologist to not hinder setup of the conventional EEG system. Patients' scalps were assessed for any skin abnormalities. Patients were treated according to local standard of care (i.e., based on clinical suspicion and conventional EEG information), and sites did not use Rapid-EEG data to alter the course of patients' treatment.

We did not collect data on whether or how the physicians used the Rapid EEG data at the bedside while waiting for conventional EEG. This was based on our assumptions that the conventional EEG in the participating sites should arrive within minutes since all sites had EEG technologists on the premises during working hours and all except one had this capacity during nights and weekends. Study coordinators detailed any device-related difficulties or any abnormalities of the patient's scalp as a result of the device, which served as our safety outcome.

The following data were collected about physicians who participated in the study: years of ICU training and years of reading conventional EEG. The following data were collected about patients: demographic information (age and sex), current administration of anti-seizure medications (yes or no), intubation status, clinical diagnosis, clinical features suggesting seizures, raw EEG data from Rapid-EEG and conventional EEG systems, and conventional EEG report detailing findings from the first day of monitoring (or until conventional EEG was disconnected, whichever came first) after the use of Rapid-EEG.

We obtained time to conventional EEG acquisition by calculating the time from the start of Rapid-EEG until the start of conventional EEG recording. We are mindful that the time from EEG order to EEG acquisition may be substantially longer. The date and time of the EEG was also used to categorize each recording as occurring during typical business hours or after-hours (including weekends).

eMethods 2: Physician questionnaire items

1. At this moment, do you think the patient is having seizures?		Yes		No	
2. What is your level of confidence about this?	1 (very low)	2 (low)	3 (medium)	4 (high)	5 (very high)
3. At this moment, would you increase the dose of anti-epileptic medications or add another anti-epileptic medication?		Yes		No	
4. What is your level of confidence about this?	1 (very low)	2 (low)	3 (medium)	4 (high)	5 (very high)

eMethods 3: Signal quality evaluation

We analyzed impedance measurements over all 10 electrodes in all subjects by calculating median and interquartile range. We also reported median [IQR] for left-sided and right-sided electrodes independently, anterior quadrant electrodes (Fp1, Fp2, F7, F8), and posterior quadrant electrodes (T5, T6, O1, O2). We calculated the percentage of time when the impedance values are above threshold (30 kOhm) for 2 consecutive measurements in each channel was calculated. The percentage of time during which impedance was out of range in two adjacent brain quadrants were also measured.

eMethod 4: Statistical Analysis

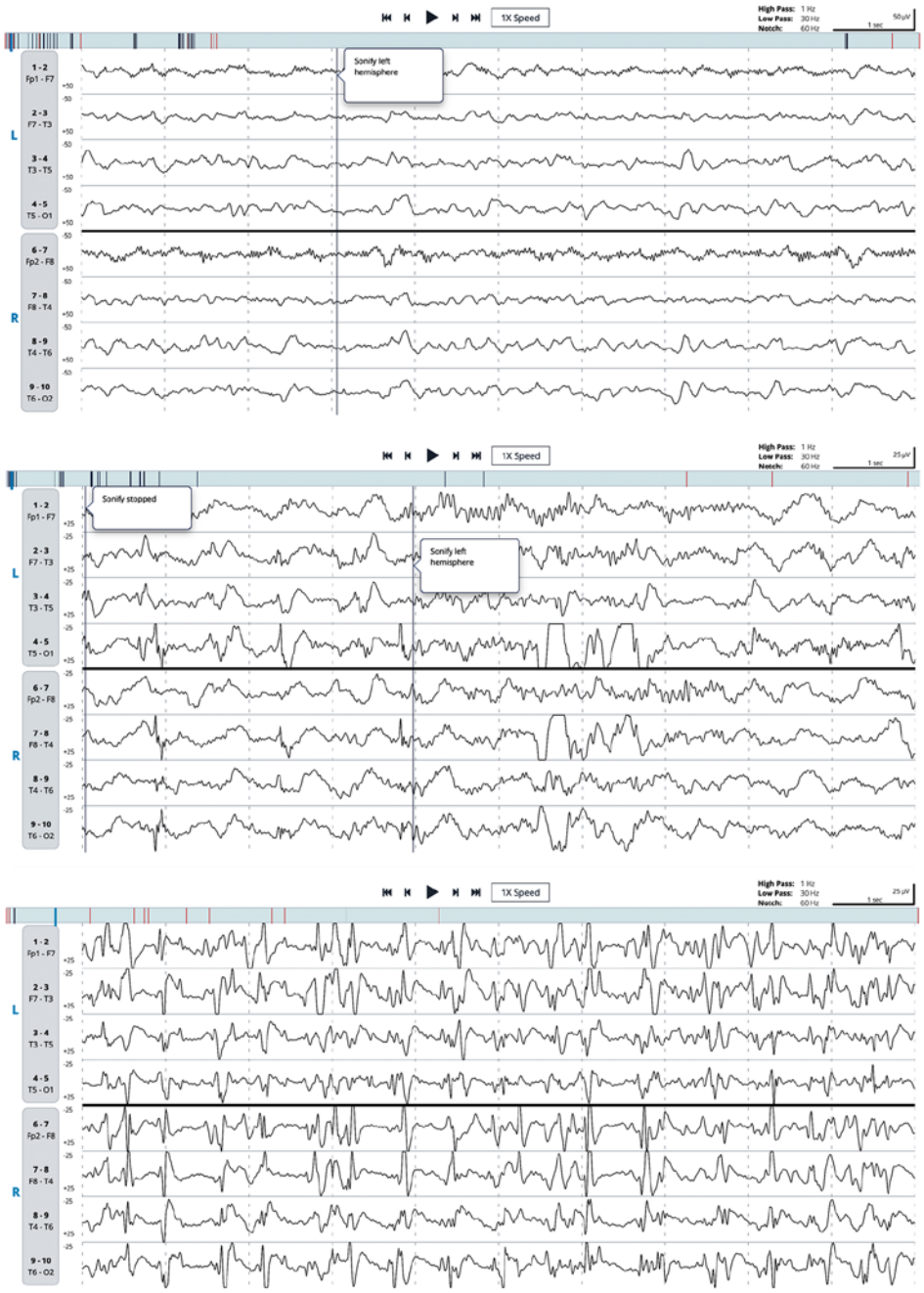
We summarized the number and proportion (with exact binomial 95% confidence intervals [CI] (2)) of changes in these items between pre- and post-Rapid-EEG assessments. McNemar test was used to test marginal heterogeneity and generate *p* values. Sensitivity and specificity measures were calculated with exact binomial 95% CIs according to established formulas (2, 3) and significance testing for the differences between pre- and post-Rapid-EEG sensitivity and specificity measures was carried out using Cochran-Mantel-Haenszel tests stratified at each individual patient level. As exploratory analysis, the impact of physician's experience on each of the 4 outcomes [i.e., diagnosis and treatment decision (Yes, No) as well as confidence (Low, High)] was assessed using separate logistic regression model by including EEG method (i.e., pre-Rapid-EEG, post Rapid-EEG) as main effect, physician's years of EEG training and years of ICU practice as numerical covariates. In addition, logistic regression analyses were applied by including EEG method (i.e., pre and post Rapid-EEG) as main effect, subgroups (pre-treatment with anti-seizure medications (Yes or No), pretreatment with intubation (Yes, No) and interaction of EEG method and subgroups as covariatess in the model. Differences in median delay of EEG acquisition were compared using Wilcoxon signed-rank test. Descriptive statistics for the ease of use for the Rapid-EEG headband and recording device were calculated at the level of the patient encounter (which was associated with a single treating physician) and at the level of the individual physician (who may have been involved in multiple patient encounters, which were averaged within-physician). Device safety, as well as indications for EEG monitoring and ICU admission, were summarized as counts and percentages.

Analysis procedures and results for the quality of Rapid-EEG signal are summarized in eMethods 2 and eFigure2 in supplementary material.

SUPPLEMENTARY FIGURES

eFigure 1. Examples of EEG pattern categories

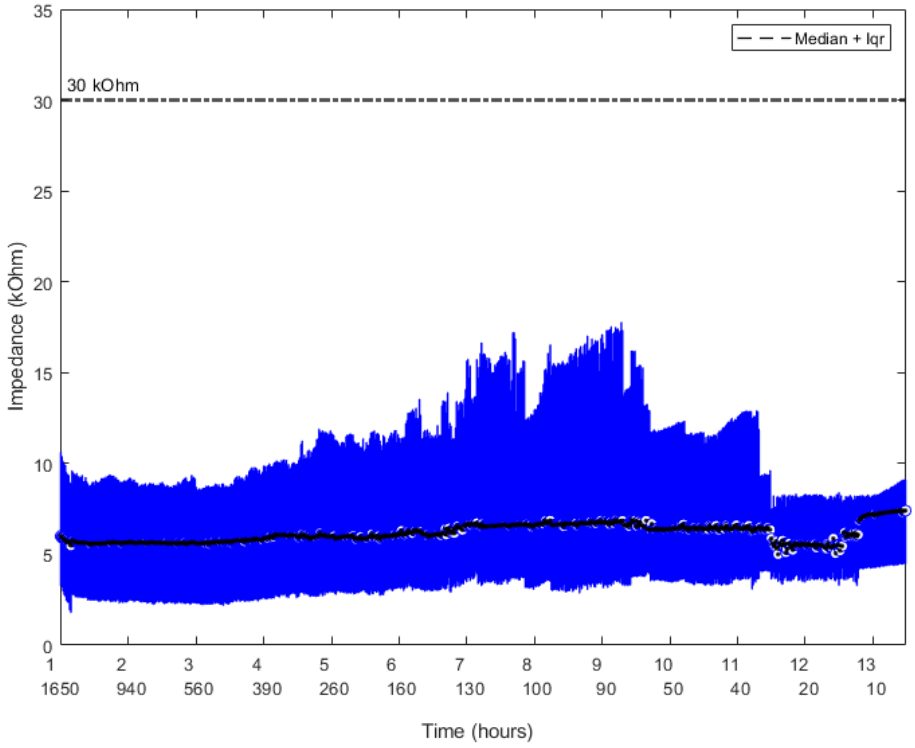
Three categories of EEG activity are shown: slow or normal activity (SL/NL, top), highly epileptiform patterns (HEP, middle), and seizure (SZ, bottom).


1X Speed
High Pass: 1 Hz
Low Pass: 30 Hz
Notch: 60 Hz
Sonify left hemisphere
Sonify stopped
1 - 2 Fp1 - F7
2 - 3 F7 - T3
3 - 4 T3 - T5
4 - 5 T5 - O1
6 - 7 Fp2 - F8
7 - 8 F8 - T4
8 - 9 T4 - T6
9 - 10 T6 - O2
L
R

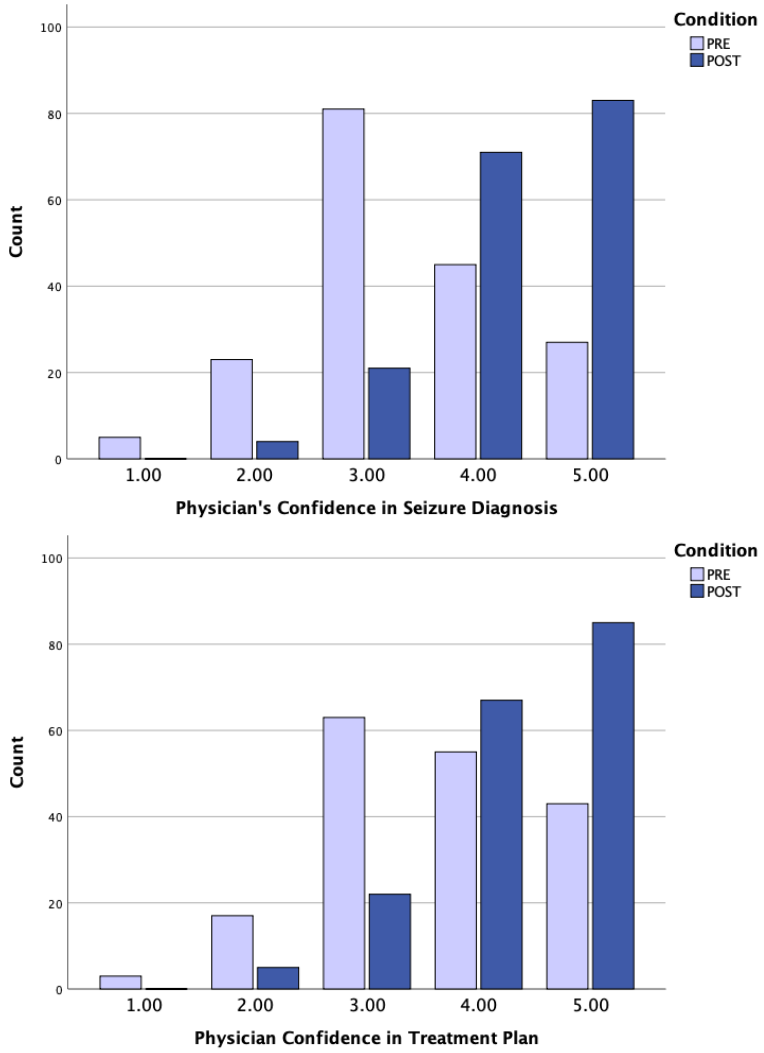
eFigure 2. Quality of Rapid-EEG signal

Quality of EEG

To measure the quality of EEG signal, we relied on the Rapid-EEG recorder's automatic electrode impedance check function, which assesses the connection quality of the EEG electrodes to the subject's scalp every 60 seconds. Using these automatic measurements, the analysis of inter-quartile range of impedance values revealed ~4.5hrs of recording with IQR of impedance within 10 kOhm while the IQR never reached the 30 kOhm values even with longer durations as long as 13.5 hours. The percentage of time when captured electrode impedances were >30kOhm was 0.43% for all electrodes in one hemisphere of the brain, 0.09% for electrodes in both anterior quadrants, and 4.85% for electrodes in both posterior quadrants.



eFigure 3. Physician confidence in diagnostic and therapeutic decision-making



SUPPLEMENTARY TABLES

eTable 1. Physician and patient characteristics

Physician Characteristics	All N=37	Site I N=14	Site II N=6	Site III N=7	Site IV N=4	Site V N=6
Years in ICU practice, median [IQR]	1.0 [1-3]	1.0 [0-1]	1.0 [1-2]	4.0 [1-5]	1.0 [1-1]	4.5 [3-6]
Years of EEG experience, median [IQR]	0.0 [0-3]	0.0 [0-2]	0.0 [0-0]	3.0 [0-4]	2.5 [2-3]	0.0 [0-5]
Patients enrolled per physician, median [IQR]	3.0 [2-6]	1.5 [1-3]	6.5 [2-13]	6.0 [4-10]	4.5 [3-6]	3.0 [2-9]
Patient Characteristics	**All N=181**	**Site I N=32**	**Site II N=47**	**Site III N=49**	**Site IV N=17**	**Site V N=36**
Age, mean (SD)	58.6 (18.7)	54.8 (19.5)	57.2 (17.6)	60.6 (18.2)	64.3 (23.0)	58.9 (17.0)
Female gender, n (%)	74 (45.1)	9 (28.1)	24 (51.1)	23 (52.3)	9 (52.9)	9 (37.5)
Receiving anti-seizure medications, n (%)	111 (69.4)	26 (81.3)	28 (59.6)	22 (78.6)	11 (64.7)	24 (66.7)
Receiving anesthetics or sedatives, n (%)	61 (37.9)	16 (50.0)	15 (31.9)	13 (44.8)	6 (35.3)	11 (30.6)
Intubated, n (%)	93 (57.1)	20 (62.5)	21 (45.7)	27 (61.4)	11 (64.7)	14 (58.3)

Data was unavailable for patients who did not provide consent. Age was unavailable for 5 patients from Site III and 12 patients from Site V. Gender was unavailable for 5 patients from Site III and 12 patients from Site V. Anti-seizure medication administration was unavailable for 21 patients from Site III. Anesthetic or sedative administration was unavailable for 20 patients from Site III. Intubation status was unavailable for 1 patient from Site II, 5 patients from Site III, and 12 patients from Site V.

eTable 2. Indications for EEG

Reasons for suspecting seizures	Number of Cases
Altered mental status	79
Seizure-like activity	39
Witnessed convulsive seizure	14
Altered mental status and seizure-like activity	12
Aphasia	10
Acute weakness	5
Cardiac arrest	2

Unspecified	3
Total	164

Clinical Diagnosis for ICU Admission	**Number of Cases**
Possible status epilepticus	52
Intracranial hemorrhage	42
Altered mental status of unknown cause	34
Brain tumor	8
Central nervous system infection/inflammation	8
Respiratory failure	6
Traumatic brain injury	5
Cardiac arrest	3
Missing	6
Total	164

eTable 3. Impact of physician experience on primary outcomes

The impact of physicians' experience in EEG and ICU on diagnosis and treatment decision was assessed using logistic regression by including setting (pre-Rapid-EEG, post-Rapid-EEG) as a main effect, years of EEG training and years of ICU practice as covariates, and the pre- and post-Rapid-EEG diagnosis/treatment plan of the same patient as repeated measurements in the model. Impact of physicians' experience on diagnostic and therapeutic confidence (1-5 scale) was assessed using a generalized linear model by including setting (pre-Rapid-EEG, post-Rapid-EEG) as a main effect, years of EEG training and years of ICU practice as covariates, and the pre- and post-Rapid-EEG confidence on the same patient's diagnosis/treatment plan as repeated measurements in the model. All regression models were performed using SAS PROC GENMOD. No multiplicity adjustments were done, and *P* values should be viewed only as descriptive.

Parameter	Response Variable	Estimate (95% CI)	P value
Years of EEG experience	Diagnosis (Yes vs. No)	-0.0717 (-0.1806, 0.0372)	0.1971
	Treatment (Yes vs. No)	-0.0765 (-0.2239, 0.0710)	0.3093
	Diagnostic confidence (1-5 scale)	-0.0018 (-0.0407, 0.0371)	0.9280
	Therapeutic confidence (1-5 scale)	-0.0344 (-0.0797, 0.0110)	0.1372
Years of ICU experience	Diagnosis (Yes vs. No)	-0.0923 (-0.1669, -0.0177)	0.0154
	Treatment (Yes vs. No)	-0.0077 (-0.0969, 0.0814)	0.8652
	Diagnostic confidence (1-5 scale)	0.0343 (0.0056, 0.0629)	0.0192
	Therapeutic confidence (1-5 scale)	0.0349 (0.0002, 0.0697)	0.0487

Greater years of ICU experience was associated with a higher rate of seizure suspicion (*P*=0.015), greater confidence in diagnostic assessments (*P*=0.019), and greater confidence in therapeutic plans (*P*=0.049).

eTable 4. Subgroup analyses according to prior treatment and intubation status

Most patients were already on anti-seizure medications (69%) and 56% were intubated (eTable 1 and eTable 2). The subgroup analyses were done for:

- Patients already treated and those who were not treated with anti-seizure medications prior to Rapid-EEG procedure.
- Patients already intubated and those who were not intubated prior to Rapid-EEG procedure.

The purpose of these subgroup analyses was to assess whether the patient's medication and intubation status affected the physicians' diagnosis or treatment decision or confidence in the two. In other words, is the impact of Rapid-EEG on physicians' behavior is different if they are assessing an intubated versus non-intubated patient, or someone who is already on anti-seizure medications versus not? The p-values presented in this table are for testing significant difference between pre and post Rapid EEG suspicion,

treatment decision, diagnostic confidence, and treatment confidence by including baseline status (i.e., prior medication status or prior intubation status) as covariate and interaction term in logistic regression model. The method was described clearer in eMethod4 section.

	Pre-Rapid-EEG n/N (%)	**Post-Rapid-EEG** n/N (%)	***P* value**
High Suspicion for Seizure = "Yes"			
Treated with ASM			<0.0001
Yes	44/111 (39.6)	16/110 (14.5)	
No	18/49 (36.7)	6/48 (12.5)	
Intubated			<0.0001
Yes	37/93 (39.8)	14/92 (15.2)	
No	26/70 (37.1)	11/69 (15.9)	
Escalate Treatment = "Yes"			
Treated with ASM			0.2234
Yes	23/111 (20.7)	17/110 (15.5)	
No	8/49 (16.3)	6/48 (12.5)	
Intubated			0.3168
Yes	20/93 (21.5)	11/92 (12.0)	
No	11/70 (15.7)	13/69 (18.8)	
Confidence in Diagnosis = "High"			
Treated with ASM			<0.0001
Yes	46/111 (41.4)	94/110 (85.5)	
No	19/49 (38.8)	45/48 (93.8)	
Intubated			<0.0001
Yes	37/93 (39.8)	80/92 (87.0)	
No	28/70 (40.0)	58/69 (84.1)	
Confidence in Treatment = "High"			
Treated with ASM			<0.0001
Yes	59/111 (53.1)	92/110 (83.6)	
No	29/49 (59.2)	44/48 (91.7)	
Intubated			<0.0001
Yes	42/93 (45.2)	78/92 (84.8)	
No	44/70 (62.9)	58/69 (84.1)	

There were no noticeable differences seen for any of those 4 outcomes between patients who were empirically treated for seizures or intubated prior to EEG vs. patients who were not. For example, in the first row, the numerator n (44) is the number of cases with High Suspicion for Seizure = Yes (i.e., the physician is highly worried that the patient is seizing) and the denominator N (111) is the total number of subjects assessed in that subgroup. The first row of summary statistics in the table indicates that the high suspicion for seizures was reported in 39.6% of cases pre-Rapid-EEG vs. 14.5% post-Rapid-EEG for the subgroup of patients who were already treated with anti-seizure medications (ASM) at baseline. The second row indicates that the high suspicion was reported for 36.7% of cases pre-Rapid-EEG vs. 12.5% post-Rapid-EEG for the subgroup of subjects who were not treated with ASM at baseline. The seizure diagnosis rate was noticeably reduced from pre-Rapid-EEG to post-Rapid-EEG in both subgroups. The p-value for overall testing of the EEG effect on seizure suspicion is <0.0001, after adjusting for the

subgroup factor (ASM status), which implies that there was a reduction in seizure diagnosis rate when combining the 2 subgroups together.

eTable 5. Ease of use analyzed at physician level

Summary statistics for Rapid-EEG headband and device ease of use were calculated for each physician by averaging across all patients evaluated by each individual physician. There were four physicians in Site I who did not provide data for ease of use, resulting in a total of 33 physicians included in the analysis. Ease of use was assessed on a five-point Likert scale (1=difficult, 5=easy); statistics presented as mean (SD).

	All N=33	**Site I N=10**	**Site II N=6**	**Site III N=7**	**Site IV N=4**	**Site V N=6**
Headband	4.4 (0.7)	4.7 (0.4)	3.9 (0.8)	4.4 (0.5)	4.4 (0.7)	4.4 (1.2)
Device	4.8 (0.3)	4.9 (0.3)	4.7 (0.4)	4.7 (0.4)	4.6 (0.5)	5.0 (0.0)

SUPPLEMENTARY REFERENCES

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