ARTICLE

Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes

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Abstract

Objective

To determine which findings on routine clinical EEGs correlate with delirium severity across various presentations and to determine whether EEG findings independently predict important clinical outcomes.

Methods

We prospectively studied a cohort of nonintubated inpatients undergoing EEG for evaluation of altered mental status. Patients were assessed for delirium within 1 hour of EEG with the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) and 3D-CAM severity score. EEGs were interpreted clinically by neurophysiologists, and reports were reviewed to identify features such as theta or delta slowing and triphasic waves. Generalized linear models were used to quantify associations among EEG findings, delirium, and clinical outcomes, including length of stay, Glasgow Outcome Scale scores, and mortality.

Results

We evaluated 200 patients (median age 60 years, IQR 48.5–72 years); 121 (60.5%) met delirium criteria. The EEG finding most strongly associated with delirium presence was a composite of generalized theta or delta slowing (odds ratio 10.3, 95% confidence interval 5.3–20.1). The prevalence of slowing correlated not only with overall delirium severity (R^2 = 0.907) but also with the severity of each feature assessed by CAM-based delirium algorithms. Slowing was common in delirium even with normal arousal. EEG slowing was associated with longer hospitalizations, worse functional outcomes, and increased mortality, even after adjustment for delirium presence or severity.

Conclusions

Generalized slowing on routine clinical EEG strongly correlates with delirium and may be a valuable biomarker for delirium severity. In addition, generalized EEG slowing should trigger elevated concern for the prognosis of patients with altered mental status.

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Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **GCS** = Glasgow Coma Scale; **GOS** = Glasgow Outcome Scale; **ICU** = intensive care unit; **OR** = odds ratio; **RASS** = Richmond Agitation Sedation Scale; **3D-CAM** = 3-Minute Diagnostic Interview for Confusion Assessment Method; **3D-CAM-S** = 3D-CAM severity.

Delirium is an acute and fluctuating disturbance of attention and awareness[1] common in neurologic practice.[2–4] Delirium is associated with dementia,[5] dependence,[6] and death[7] but can be underrecognized.[8] While clinical tools can standardize delirium assessment,[9,10] they involve subjective and intermittent evaluation of a complex, dynamic condition that generates disagreement even among experts.[11] There is increasing concern that delirium severity is more clearly associated with worse prognosis,[12] even among patients with only subsyndromal delirium.[13,14] Therefore, biomarkers of delirium severity could be clinically important.

Early studies demonstrated that EEG can be associated with delirium presence[15–17] and severity.[18–20] In carefully selected cohorts without neuropsychiatric disease, EEG slowing, measured as increased delta and theta frequency power or decreased alpha frequency power, can be ≥90% sensitive and specific for delirium.[16] Slowing may not be as accurate in more typical populations with varied causes of altered mental status, however, because slowing can also be observed with decreased arousal, including coma, sleep, and sedation.[21] It remains unclear whether EEG slowing identifies only hypoactive delirium or whether it identifies delirium with normal arousal or hyperactive presentations.[1]

We studied whether routine clinical EEG findings, including slowing, are correlated with delirium severity in a heterogeneous population with various causes of altered mental status. We also studied whether slowing is present only in patients with decreased arousal or reflects delirium more broadly. Lastly, we studied whether EEG slowing provides additional prognostic information compared to delirium assessment about important clinical outcomes such as length of stay, functional outcome, and mortality.

Methods

Patient cohort

We conducted a prospective, observational cohort study of adult, nonintubated inpatients referred for EEG testing in the course of routine clinical care at a tertiary care academic medical center. The study was undertaken as part of a quality improvement initiative with a plan for interval assessment after 12 months, which determined the study size. The eventual study period was 17 months.

From August 2015 to December 2016, nonintubated adult inpatients referred for clinical EEG testing were screened daily for enrollment. Patients were included if they were referred for EEG for evaluation of altered mental status, as per the primary team's clinical order. Patients were considered for evaluation from all wards, including the medical, surgical, and neurologic floors, as well as intensive care units (ICUs) if patients were not intubated. Patients were excluded before evaluation if they could not be assessed within 1 hour of EEG recording, had a recorded history of dementia, were deaf, were aphasic, or did not speak English. Because at least some exclusion criteria were not clinical, i.e., dependent on timing of staff availability, we maintained strict records of only the patients who were actually evaluated in-person. A small number of patients were identified as having dementia after evaluation but before data analysis. These patients were recorded and excluded at this second stage before analysis, as noted in the Results section. Patients were also excluded at this stage if there were technical difficulties with EEG that precluded clinical interpretation.

Standard protocol approvals, registrations, and patient consents

This study of human patients was approved by the Institutional Review Board at Massachusetts General Hospital (Boston), including review of EEG and other clinical data. The Partners Healthcare Human Research Committee provided a waiver of consent for this study.

Clinical assessment

Within 1 hour of clinical EEG recording, patients were assessed at the bedside by study staff. Study staff were unaware of the EEG results at the time of delirium assessment. Staff were trained to perform assessments through a combination of didactics, literature review, in-person case reviews, and ongoing discussions. Patients were evaluated with a structured cognitive assessment that included standardized questions and structured prompts for evaluator observations to measure delirium presence with the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM)[10]–defined delirium and delirium severity with the 3D-CAM severity (3D-CAM-S) scoring method.[22] Responses to individual questions were considered normal only if there was an unequivocally correct response. In cases when a patient did not answer a question, the question was repeated. If questions remained unanswered (including as a result of a decreased level of arousal), nonanswers were scored as incorrect.

The primary tool for delirium assessment was the 3D-CAM because of its operationalized and reproducible implementation of the CAM algorithm for delirium ascertainment.[10] The 3D-CAM has a validated sensitivity and specificity of >90% for delirium. Similarly, the primary tool for scoring delirium

severity was the 3D-CAM-S, which predicts clinical outcomes such as length of stay and strongly corresponds to other measures of delirium severity.[22] These tools measure and score the severity of 4 individual features: (1) acute change/fluctuating course, 0 to 1 points; (2) inattention, 0 to 2 points; (3) disorganized thinking, 0 to 2 points; and (4) altered level of consciousness, 0 to 2 points. Changes in mental status from baseline were assessed by chart review and nursing input; family input was also taken into account when available. Similar to other CAM algorithms,[9] the presence of delirium was defined by the presence of features 1 and 2, with the additional presence of either feature 3 or 4. The severity of delirium is scored as the sum of the severity of all 4 features (total 0–7 points).

Patients were also evaluated with other scales, including the Glasgow Coma Scale (GCS; normal arousal score 15)[23] and Richmond Agitation Sedation Scale (RASS; normal arousal score 0)[24] to assess their level of arousal. The RASS level of arousal was additionally stratified into 4 groups: −5 to −4 represented a coma-like state; −3 to −1 represented a hypoactive state; 0 represented an alert and calm state; and +1 to +4 represented a hyperactive state. The Charlson Comorbidity Index score was calculated from the medical record.[25] Patient records were also screened after discharge to determine the Glasgow Outcome Scale (GOS) score at hospital discharge (1 = death, 5 = good recovery)[26] with a combination of discharge physician documentation and physical and occupational therapy evaluations at discharge.[27] Given the inpatient design of the study, no patients were lost to follow-up.

EEG recordings and interpretation

Routine clinical EEGs were recorded with Ag/AgCl scalp electrodes using the standard international 10- to 20-electrode placement by qualified EEG technicians and read and reported clinically by neurophysiologists. EEGs and patient evaluation happened within 1 hour of each other, and patient evaluation happened before the EEG was clinically interpreted. As part of routine clinical practice, all EEG recordings were reviewed by 2 clinical experts (fellow and attending physician electroencephalographers) before reports were finalized and published in the electronic medical record system. Although clinical EEG readers had access to routine clinical data, they were blinded to the results of the research evaluation.

Clinical EEG reports were reviewed to identify the presence of various findings: posterior dominant rhythm, theta slowing (generalized or focal), delta slowing (generalized or focal), generalized rhythmic delta activity, lateralized rhythmic delta activity, sporadic discharges, periodic discharges (generalized or lateralized), generalized periodic discharges with triphasic morphology (triphasic waves), low-voltage/generalized attenuation, and burst suppression. Generalized EEG slowing was a composite measure defined as the presence of either generalized (i.e., not focal) theta or generalized delta slowing.

Additional chart review

Medical records were additionally reviewed by an investigator who had not evaluated the patient or been involved with EEG recordings to identify the clinically diagnosed syndromes causing altered mental status. Clinical syndromes were identified from primary team and consultation notes discussing the patient's status on the day of EEG recording. Clinical syndromes included ongoing delirium, resolved delirium, seizures (either ongoing or prior/postictal), psychiatric disease (mania, psychosis, depression, anxiety, or psychogenic nonepileptic spells), syncope and other spells that could not be otherwise specified, stroke, mass or increased intracranial pressure including traumatic brain injury, encephalitis (infectious or autoimmune), suspected neurodegenerative disease, and transient global amnesia. More than 1 clinical syndrome could be associated with altered mental status. Specific contributors to delirium were also identified from the clinical notes with a modified version of the Delirium Etiology Checklist.[28] Specific groups of etiologies identified were metabolic (including hepatic, renal, respiratory, cardiac, gastrointestinal, and electrolyte abnormalities), drug related (illicit intoxication, alcohol or benzodiazepine withdrawal, or iatrogenic sedatives), infection (systemic, not CNS), and neurologic disease (including CNS infection).

Statistical analysis

Proportions, medians, and interquartile ranges were calculated for descriptive analysis given that most of the data were not normally distributed. Groups were compared with nonparametric Wilcoxon rank-sum tests. Two or more proportions were compared with the Pearson χ^2 tests of multiple proportions. The significance level for all tests was set at $p < 0.05$. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of different EEG features for delirium were assessed primarily with the results of the 3D-CAM assessment as the delirium reference. For supplementary analyses, subsyndromal delirium was defined as the presence of 2 or more 3D-CAM features without meeting full 3D-CAM criteria for delirium. In addition, the clinical diagnosis of altered mental status due to ongoing delirium was also used as a delirium reference when specified in supplementary analyses. Positive likelihood ratios were calculated as sensitivity/(1 − specificity) and negative likelihood ratios as (1 − sensitivity)/specificity. The significance of likelihood ratios was determined by computing bootstrap distributions 1,000 times and evaluating whether 2-tailed 95% confidence intervals (CIs) included the value of 1.

The relationship between 3D-CAM-S severity and generalized EEG slowing was assessed with linear regression. The population was stratified by 3D-CAM-S severity scores (0–7) and the prevalence of generalized EEG slowing for each stratum was calculated. CIs for prevalences were determined using 1,000 bootstraps. Similar analyses were performed for each of the four 3D-CAM-S features individually. Patients were also stratified by level of arousal by the GCS or RASS,

and the proportions of EEG slowing stratified by level of arousal were compared with proportion tests.

The associations among EEG slowing, delirium status, and clinical outcomes of length of stay or GOS scores were first assessed with rank-based estimation for linear models, a nonparametric analysis of variance (ANOVA), given the nonnormality of the data (Rfit in R, R Foundation for Statistical Computing, Vienna, Austria).[29] Adjusted multivariable linear and logistic regression was then used to study the relationship between generalized EEG slowing and clinical outcomes with the following covariates: 3D-CAM-S delirium severity, age, sex, and Charlson Comorbidity Index score. Linear regression was used to assess associations of EEG slowing with length of stay and GOS scores, and results are reported as β coefficients. Delirium contributors were also used as covariates in supplementary analyses when specified. Due to quasi-complete separation between EEG slowing and mortality, Firth bias-reduced logistic regression had to be applied to quantify the association among EEG slowing, mortality, and the covariates.[30,31] Results of the logistic regressions are reported as β coefficients or odds ratios (ORs) when indicated. Proportion/Pearson χ^2 tests, rank-based estimation for linear models, and Firth bias-reduced logistic regression were performed in R.[32] All other analyses were performed in MATLAB (MathWorks, Natick, MA).

Data availability

All supplementary data are available from the Dryad Digital Repository (doi.org/10.5061/dryad.tv06pt2). Further anonymized data can be made available to qualified investigators on request to the corresponding author.

Results

Patient characteristics

We studied the relationship between routine clinical EEG findings and delirium in a prospective cohort of nonintubated patients being evaluated for altered mental status. Of the 210 patients initially assessed, 10 were subsequently excluded: 8 due to a prior diagnosis of dementia that was determined after the evaluation but before data analysis and 2 due to technical difficulties with the EEG. Of the total of 200 patients analyzed, 121 patients (60.5%) screened positive for delirium by 3D-CAM criteria.

Patients with delirium were more clinically ill and had worse outcomes (table 1). Patients with delirium were older and had lower RASS and GCS scores, longer hospital stays, higher Charlson Comorbidity Index scores, and lower GOS scores at discharge. They also had higher 3D-CAM-S severity scores and were more likely to experience in-hospital mortality. They were more likely to be admitted to an ICU and less likely to be admitted and discharged from the observation unit (an inpatient ward managed by emergency department staff and often comanaged by consultants). Approximately 80% of patients were admitted to standard floor services, and most were admitted to medicine or neurology services. Admission diagnoses were heterogeneous, and 38% of patients were admitted with a primary concern of altered mental status.

We also reviewed the clinically determined etiologies of altered mental status. Ongoing delirium was clinically identified in 59% of patients (118 of 200) compared to 60.5% (121 of 200) with the 3D-CAM criteria. There was 73.5% concordance between the extracted clinical diagnosis of ongoing delirium and 3D-CAM ascertainment. Ongoing delirium was the only clinical altered mental status syndrome significantly more likely in patients with delirium by 3D-CAM criteria (table e-1 available from Dryad, doi.org/10.5061/dryad.tv06pt2). In contrast, syndromes less likely to occur in patients with 3D-CAM–defined delirium included resolved delirium, psychiatric disease, and syncope or spells not otherwise specified.

EEG features and delirium status

We examined the associations between EEG features and delirium status (table 2). Several EEG features were associated with 3D-CAM–defined delirium with >90% specificity such as triphasic waves (98.7% specific, OR 8.6, 95% CI 1.1–67.4). However, specific features such as triphasic waves were not sensitive for delirium in our cohort and were relatively rare: only 12 of 121 patients screening positive for delirium had triphasic waves (sensitivity 9.9%).

In contrast to highly specific but uncommon EEG findings, multiple measures of generalized slowing were much more common and associated with delirium. Generalized slowing in the theta or delta frequency ranges was strongly associated with delirium (theta slowing: OR 6.8, 95% CI 3.6–12.7, sensitivity 73.6%, specificity 70.9%; delta slowing: OR 7.4, 95% CI 3.8–14.4, sensitivity 65.3%, specificity 79.7%), as was the absence of a posterior dominant rhythm >8 Hz (OR 6.4, 95% CI 3.4–11.9, sensitivity 71.1%, specificity 72.2%). A composite measure of EEG slowing, defined as either generalized theta or generalized delta slowing, had the highest significant diagnostic OR for delirium (10.3, 95% CI 5.3–20.1).

To determine the clinical altered mental status syndromes associated with generalized EEG slowing, we analyzed the likelihood of observing each clinical altered mental status syndrome for patients with and without generalized EEG slowing (table e-2 available from Dryad, doi.org/10.5061/dryad.tv06pt2). Ongoing delirium was the only clinical altered mental status syndrome significantly more common in patients with EEG slowing (OR 6.5, 95% CI 3.4–12.2). The only clinical syndromes that were significantly less common in patients with EEG slowing were psychiatric disease (OR 0.1, 95% CI 0.0–0.2) and syncope or spells (OR 0.2, 95% CI 0.1–0.8).

Generalized EEG slowing and delirium severity

To determine the relationship between EEG features and delirium severity, we identified patients with subsyndromal

Table 1 Patient characteristics based on 3D-CAM defined delirium

Quantitative data, median (IQR)	No delirium (n = 79)	Delirium (n = 121)	*p* Value (rank sum)
Age, y	55 (37.25–69)	62 (54–73.25)	0.009
Charlson Comorbidity Index score	2 (1–5)	4 (2–5)	0.02
Delirium severity (3D-CAM-S score 0–7)	1 (0–2)	5 (4–7)	<0.001
RASS score (−5 to +4)	0 (0–0)	−1 (−2 to 0)	<0.001
GCS score (3–15)	15 (15–15)	13 (10–15)	<0.001
Length of stay, d	6 (3.25–10)	14 (7–23)	<0.001
GOS score at discharge (1–5)	4 (3–5)	3 (3–4)	<0.001
Categorical data, % (n)	**No delirium (n= 79)**	**Delirium (n=121)**	***p* Value (χ^2)**
Sex (female)	48.1 (38)	40.5 (49)	0.289
Hospital mortality	2.5 (2)	16.5 (20)	0.002
ICU admission	3.8 (3)	13.2 (16)	0.026
Primary team			
Medicine	35.4 (28)	47.9 (58)	0.081
Neurology	34.2 (27)	30.6 (37)	0.594
Neurosurgery	2.5 (2)	9.1 (11)	0.066
Psychiatry	5.1 (4)	1.7 (2)	0.167
Surgery	5.1 (4)	5.0 (6)	0.974
Observation unit	17.7 (14)	5.8 (7)	0.007
Admission diagnoses			
Altered mental status	36.7 (29)	38.8 (47)	0.761
Seizure	19.0 (15)	16.5 (20)	0.655
Neurovascular	11.4 (9)	19.0 (23)	0.151
Neurooncology	1.3 (1)	8.3 (10)	0.034
Neurology (other)	34.2 (27)	29.8 (36)	0.510
Psychiatric disorders	12.7 (10)	9.9 (12)	0.545
Infection	12.7 (10)	9.1 (11)	0.421
Cardiovascular	7.6 (6)	4.1 (5)	0.294
Hematology/oncology	5.1 (4)	5.8 (7)	0.827
Gastrointestinal	3.8 (3)	6.6 (8)	0.393
Respiratory	2.5 (2)	2.5 (3)	0.982
Renal disease	1.3 (1)	3.3 (4)	0.366
Elective surgery	2.5 (2)	1.7 (2)	0.664
Trauma	2.5 (2)	9.9 (12)	0.045
Other	5.1 (4)	2.5 (3)	0.331

Abbreviations: GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICU = intensive care unit; IQR = interquartile range; RASS = Richmond Agitation Sedation Scale; 3D-CAM-S = 3-Minute Diagnostic Interview for Confusion Assessment Method severity.
Quantitative data in the top part of the table are reported as median (IQR) and compared with rank-sum tests. Categorical data for the bottom part of the table are reported as percentages (n = counts) and compared with χ^2 tests of proportions. Tests were not corrected for multiple comparisons given the descriptive nature of these analyses. The observation unit is an inpatient ward managed by emergency department staff. Admission diagnoses percentages add up to >100% because patients could have >1 admission diagnosis.

Table 2 Associations between routine clinical EEG features and delirium

		Association with delirium				
	Prevalence, %	Sensitivity, %	Specificity, %	LR+	LR−	OR (95% CI)
Absent posterior dominant rhythm	54.0	71.1	72.2	2.55[a]	0.40[a]	6.4 (3.4–11.9)
Generalized slowing (theta or delta)	63.5	83.5	67.1	2.54[a]	0.25[a]	10.3 (5.3–20.1)
Theta slowing, generalized	56.0	73.6	70.9	2.53[a]	0.37[a]	6.8 (3.6–12.7)
Theta slowing, focal	13.0	16.5	92.4	2.18	0.90	2.4 (0.9–6.3)
Delta slowing, generalized	47.5	65.3	79.7	3.22[a]	0.44[a]	7.4 (3.8–14.4)
Delta slowing, focal	26.5	29.8	78.5	1.38	0.90	1.5 (0.8–3.0)
Rhythmic delta activity, generalized	10.0	12.4	93.7	1.96	0.94	2.1 (0.7–6.0)
Rhythmic delta activity, lateralized	1.0	0.8	98.7	0.65	1.00	0.7 (0.0–10.5)
Sporadic discharges	15.0	20.7	93.7	3.26[a]	0.85[a]	3.9 (1.4–10.5)
Periodic discharges, generalized	4.0	6.6	100.0	>10[a]	0.93[a]	Inf (0–Inf)
Periodic discharges, lateralized	6.5	8.3	96.2	2.18	0.95	2.3 (0.6–8.6)
Triphasic waves	6.5	9.9	98.7	7.83[a]	0.91[a]	8.6 (1.1–67.4)
Low-voltage/generalized attenuation	1.5	1.7	98.7	1.31	1.00	1.3 (0.1–14.7)
Burst suppression	0	NA	NA	NA	NA	NA

Abbreviations: CI = confidence interval; Inf = infinite; LR = likelihood ratio; NA = not applicable; OR = odds ratio.
For each EEG feature, we report the overall prevalence, sensitivity, specificity, positive LR, negative LR, and diagnostic OR with 95% CI for 3-Minute Diagnostic Interview for Confusion Assessment Method–defined delirium. The significance of LRs was determined by computing bootstrap distributions. Generalized slowing was a composite measure of either generalized theta or delta slowing. Burst suppression was not observed in any patient in this study.
[a] $p < 0.05$

delirium, who had ≥2 features of 3D-CAM–defined delirium without meeting full criteria. Patients with subsyndromal delirium had intermediate rates of EEG slowing compared to patients without delirium or those meeting full criteria for delirium (table e-3 available from Dryad, doi.org/10.5061/dryad.tv06pt2). We further stratified patients according to 3D-CAM-S scores (0 = least severe, 7 = most severe). Examination of EEG findings across all patients suggested that generalized slowing was more likely to occur with increasing delirium severity (figure 1). We calculated the proportion of patients who had generalized theta or delta slowing at each level of delirium severity (figure 2). Delirium severity correlated strongly with the prevalence of generalized EEG slowing ($R^2 = 0.907$, $p < 0.001$).

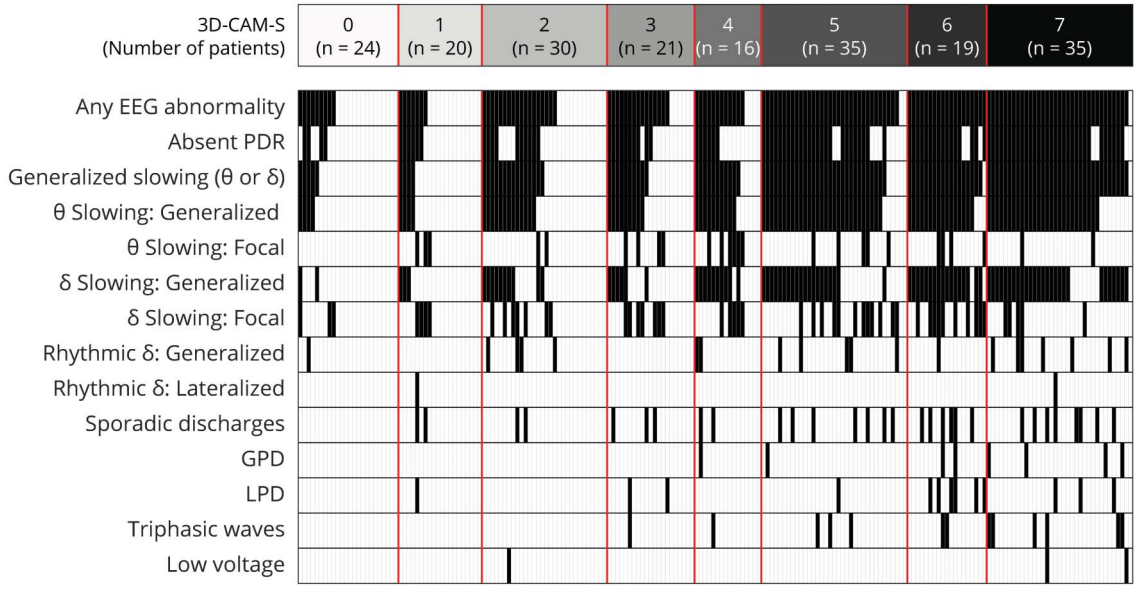
We further confirmed that generalized slowing remained significantly associated with delirium severity even after adjusting for age, sex, and Charlson Comorbidity Index score (table 3, left). The delirium severity scores were almost 3 points worse for patients with generalized slowing compared to those without (adjusted multivariate $\beta = 2.81$, $p < 0.001$).

Because delirium has multiple clinical features, we next examined whether the association between generalized EEG slowing and delirium severity was driven solely by any single individual feature of delirium such as more severe alterations in the level of consciousness. CAM-based algorithms for delirium such as the 3D-CAM-S score the severity of 4 core features of delirium: acute change/fluctuating course, inattention, disorganized thinking, and altered level of consciousness. We found that the prevalence of EEG slowing was correlated with increasing severity in all 4 core delirium features (figure 2).

Generalized EEG slowing and level of arousal in delirium

Because EEG slowing can be associated with decreased arousal in other contexts such as sleep or sedation, we investigated whether the relationship between EEG slowing and delirium was driven primarily by decreased arousal. We performed subgroup analyses on patients with specified levels of arousal. We first examined whether the prevalence of generalized EEG slowing in patients with delirium varied across levels of arousal as assessed by the RASS (figure 3A). We stratified patients into 4 RASS groups: −5 to −4 represented coma-like states; −3 to −1 represented hypoactive states; 0 represented an alert and calm state; and +1 to +4 represented hyperactive states. Statistically, the proportion of EEG slowing did not differ significantly among these strata in a 4-sample test for equality of proportions (Pearson $\chi^2 = 6.69$, $p = 0.083$). More specifically, the proportion of EEG slowing in hypoactive patients (RASS score −3 to −1) was similar to that in hyperactive patients (RASS score +1 to +4) ($\chi^2 = 0.01$, $p = 0.912$).

Figure 1 Prevalence of EEG features by delirium severity for all patients



Patients were stratified by delirium severity as indicated in the top row (3-Minute Diagnostic Interview for Confusion Assessment Method severity [3D-CAM-S] scores 0–7). The figure below represents EEG feature data from all patients, with each feature represented by a row and each patient represented by a single column. A black cell indicates the presence of the EEG feature for that patient, whereas a white cell indicates the absence of the feature for that patient. Within each stratum, for display purposes, patients are sorted according to the presence of generalized slowing. GPD = generalized periodic discharges; LPD = lateralized periodic discharges; PDR = posterior dominant rhythm.

Because there appeared to be a possible, nonsignificant U-shaped trend with the lowest levels of EEG slowing in patients with normal arousal, we also analyzed whether delirium is associated with generalized EEG slowing even in patients with only normal levels of arousal, as assessed by either the RASS (score 0; figure 3B) or GCS (score 15; figure 3C). For both measures of normal arousal, generalized EEG slowing was significantly more prevalent among patients who screened positive for delirium than patients who screened negative.

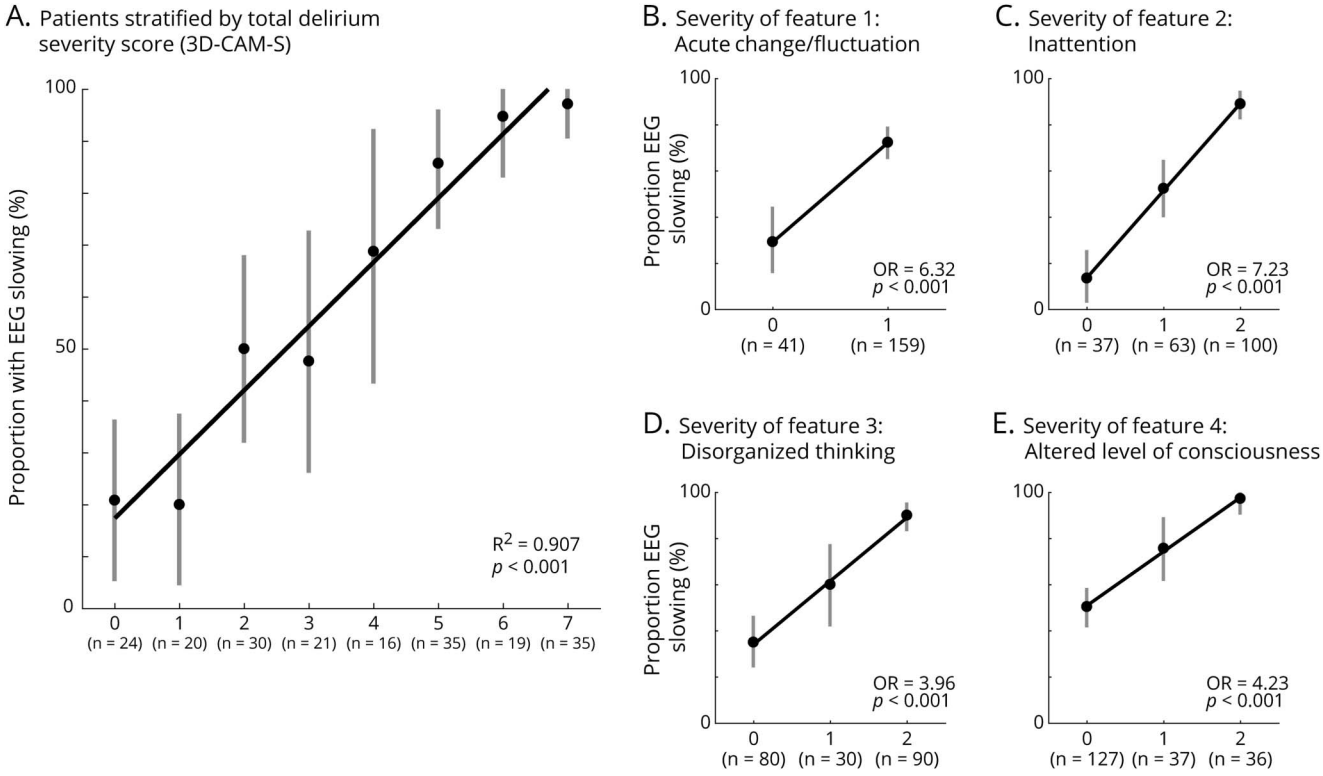
Generalized EEG slowing and clinical outcomes

Delirium has been associated with worsened clinical outcomes, including increased length of stay, decreased independence at discharge, and increased mortality.[33] We examined whether EEG slowing was also associated with these outcomes (figure 4). Both EEG slowing and delirium status were significantly associated with increased length of stay (robust rank estimation for linear models/ANOVA: EEG slowing $F = 17.9$, $p < 0.001$; delirium $F = 11.9$, $p < 0.001$; no significant interaction $F = 2.9$, $p = 0.092$; figure 4A). The median length of stay for patients with EEG slowing was 8 days longer overall than for patients without EEG slowing (median 14 vs 6 days, rank-sum $p < 0.001$). Even after adjustment for delirium severity, age, sex, and Charlson Comorbidity Index, patients with generalized EEG slowing stayed 8.6 days longer than those without ($\beta = 8.622$, $p = 0.008$; table 3, right).

EEG slowing and delirium status were also significantly associated with worse functional outcomes as measured by the GOS (robust rank estimation for linear models/ANOVA: EEG slowing $F = 7.2$, $p = 0.008$; delirium $F = 8.8$, $p = 0.003$; no significant interaction $F = 0.08$, $p = 0.774$; figure 4B). The median GOS score was approximately 1 point worse overall for patients with EEG slowing than for patients without (median score of 3 vs 4, rank-sum $p < 0.001$). Even after adjustment for multiple covariates, including delirium severity, patients with generalized EEG slowing had GOS scores that were 0.4 points worse than the scores of patients without slowing ($\beta = -0.402$, $p = 0.023$; table 3, right). Results for both length of stay and functional outcomes were similar when clinical diagnosis was used as the reference standard for delirium (figure e-1 available from Dryad, doi.org/10.5061/dryad.tv06pt2).

We also reviewed the medical record for all delirious patients to extract etiologic factors that contributed to their delirium (table e-4 available from Dryad, doi.org/10.5061/dryad.tv06pt2). At least 75% of patients with each contributing factor had EEG slowing. However, because delirium can be multifactorial, we applied multivariable logistic regression and found that only infection and metabolic contributions to delirium were independently associated with EEG slowing. Delirium contributors did not affect the association of clinical delirium and EEG slowing with clinical outcomes when used as linear regression covariates (length of stay: clinical delirium: $\beta = 10.71$, $p = 0.009$; EEG slowing: $\beta = 8.72$, $p = 0.003$; GOS score: clinical delirium: $\beta = -0.60$, $p = 0.007$; EEG slowing: $\beta = -0.54$, $p < 0.001$).

Figure 2 Prevalence of generalized EEG slowing was correlated with delirium severity



(A) Patients were stratified by 3-Minute Diagnostic Interview for Confusion Assessment Method delirium severity (3D-CAM-S) scores, and the prevalence of generalized EEG slowing was calculated at each score. Black line indicates fit by linear regression (adjusted $R^2 = 0.907$, $p < 0.001$). Gray vertical lines indicate the bootstrap confidence intervals for each stratum (2.5%–97.5% percentiles of 1,000 bootstraps). (B–E) Patients were additionally stratified by the severity score of each individual 3D-CAM-S delirium feature (1–4), and the prevalence of generalized EEG slowing was calculated at each score. Logistic regression was used to quantify the relationship between delirium feature severity (dependent variable) and EEG slowing (independent variable). Severity of each delirium feature was significantly associated with EEG slowing (all odds ratio [OR] > 1, $p < 0.05$).

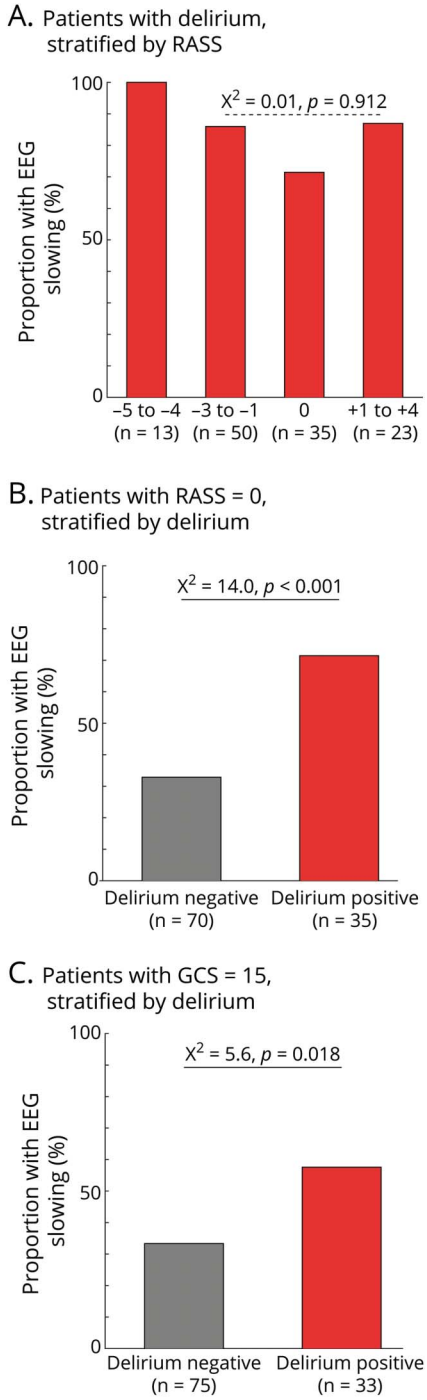
Lastly, EEG slowing was associated with increased in-hospital mortality. Rates of mortality differed depending on EEG slowing (4-sample test for equality of proportions: $\chi^2 = 14.1$, $p = 0.003$; figure 4C). None of the 73 patients without EEG slowing died in the hospital, including even those who screened positive for delirium. In contrast, 19 of

Table 3 Association among generalized EEG slowing, delirium severity, and clinical outcomes

	Delirium severity				Clinical outcomes					
	Univariate analysis		Adjusted multivariate analysis		Length of stay		GOS		Mortality	
Clinical features	β Value	*p* Value	β Value	*p* Value	β Value	*p* Value	β Value	*p* Value	β Value	*p* Value
Generalized EEG slowing	2.88	<0.001	2.81	<0.001	8.622	0.008	−0.402	0.023	3.146	0.000
Age	0.03	0.001	0.02	0.139	−0.105	0.367	−0.004	0.532	−0.038	1.000
Sex (female)	−0.29	0.389	−0.12	0.664	4.514	0.071	0.101	0.460	−0.070	1.000
Charlson Comorbidity Index	0.22	0.006	−0.11	0.339	−0.077	0.939	−0.081	0.140	1.169	1.000
3D-CAM-S delirium severity	NA	NA	NA	NA	1.576	0.015	−0.161	<0.001	1.310	1.000

Abbreviations: GOS = Glasgow Outcome Scale; NA = not applicable; 3D-CAM-S = 3-Minute Diagnostic Interview for Confusion Assessment Method severity. Left side of table: the relationships between delirium severity and EEG slowing, age, sex, and the Charlson Comorbidity Index were calculated with linear regression using both univariate and adjusted multivariable models. Results are displayed as the β coefficients and *p* values for coefficients. Generalized EEG slowing result was significantly associated with delirium severity in both univariate and adjusted multivariable models. 3D-CAM-S was not included as an independent variable in this model (NA) but was included in subsequent models. Right side of table: generalized EEG slowing predicted poor clinical outcomes, specifically increased length of stay, worse GOS scores at discharge, and increased mortality, even after adjustment for covariates, including delirium severity. Results are displayed as the β coefficients and *p* values from multivariable adjusted regression models (length of stay and GOS score: linear regression; mortality: logistic regression). Due to quasi-complete separation between EEG slowing and mortality, the Firth bias-reduced logistic regression had to be applied in this analysis, yielding EEG slowing as the only significant predictor of mortality in the logistic regression.

Figure 3 EEG slowing was increased in delirium even in patients with normal levels of arousal



(A) Prevalence of EEG slowing was calculated for patients with 3-Minute Diagnostic Interview for Confusion Assessment Method–defined delirium within 4 levels of arousal. Arousal was stratified by Richmond Agitation Sedation Scale (RASS) scores: −5 to −4 represent coma-like states; −3 to −1 represent hypoactive delirium states; 0 represents an alert and calm state; and +1 to +4 represent hyperactive delirium states. Proportions of EEG slowing did not differ significantly among these 4 strata (Pearson $\chi^2 = 6.69$, $p = 0.076$). More specifically, proportion of EEG slowing did not differ between patients with hypoactive and hyperactive levels of arousal ($\chi^2 = 0.01$, $p = 0.921$). (B–C) We also compared the prevalence of EEG slowing between patients with and without delirium at normal levels of arousal (B, RASS value of 0; C, Glasgow Coma Scale [GCS] value of 15). EEG slowing was more prevalent among patients who screened positive for delirium than those who screened negative with either measure of normal arousal (B, RASS = 0: $\chi^2 = 14.0$, $p < 0.001$; C, GCS = 15: $\chi^2 = 5.6$, $p = 0.018$).

127 patients with EEG slowing died in the hospital (mortality 15%, sensitivity 100%, specificity 40.3%). EEG slowing was associated with increased mortality in patients both with and without delirium (figure 4C). Due to quasi-complete separation between EEG slowing and mortality, the Firth bias-reduced logistic regression had to be applied to quantify the association among EEG slowing, various covariates, and mortality; EEG slowing was the only significant predictor of mortality in the multivariable model (table 3, right).

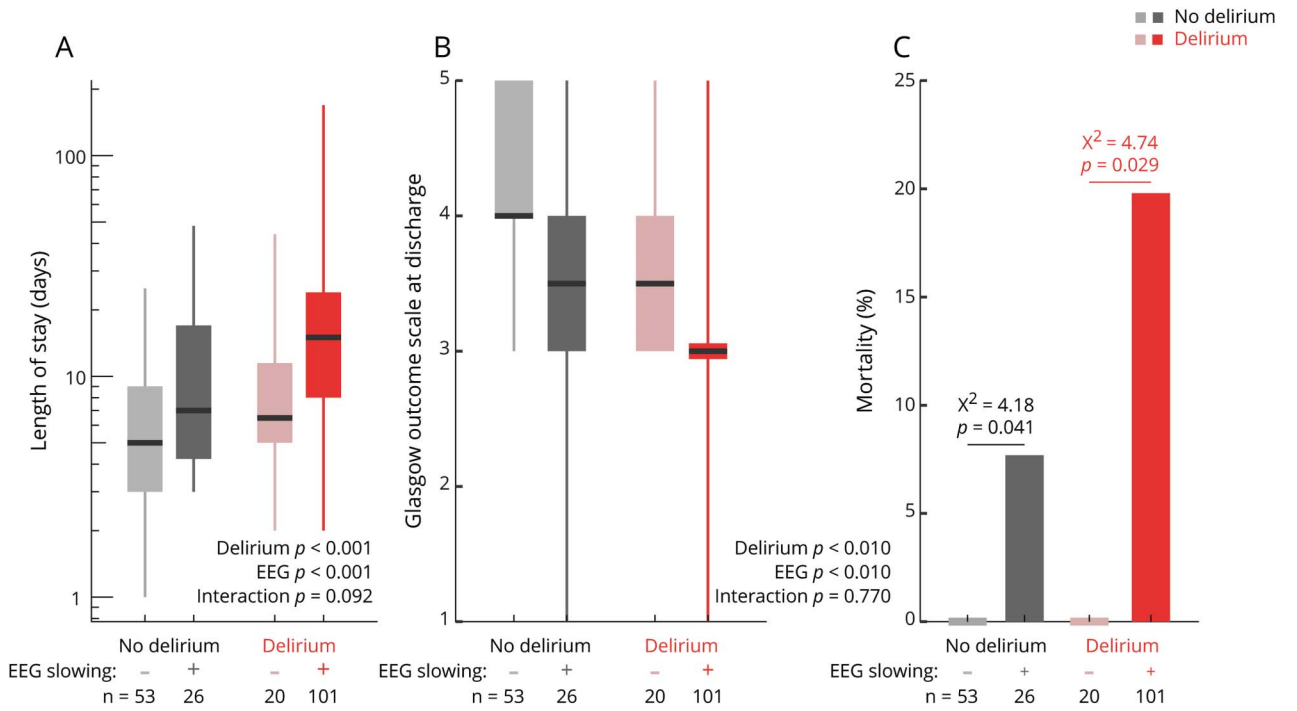
Discussion

In this prospective study of nonintubated adult inpatients, routine clinical EEG findings were associated with delirium presence and severity. Specifically, generalized theta or delta EEG slowing showed strong and systematic correlations with delirium severity across various types of delirium presentations. In addition, generalized EEG slowing predicted poor clinical outcomes, including increased length of stay, worse GOS scores, and increased mortality, even after accounting for delirium severity and other covariates.

The sensitivity and specificity of EEG slowing for delirium have previously been reported to be ≥95%, but these high values were obtained in quantitative analysis in a carefully selected, homogeneous cohort of postsurgical patients.[16] In our more varied patient population, a composite, qualitative measure of routine, generalized slowing was strongly associated with delirium (OR 10.3), with high sensitivity (83.5%) but lower specificity (67.1%). The specificity of EEG slowing for delirium will always depend at least in part on the prevalence of confounding states in control cohorts such as sedation and a variety of pathologic brain lesions.[21,34] These states may be more difficult to exclude in more typically heterogeneous patient populations, including those at the highest risk of delirium. Nevertheless, we found that generalized EEG slowing was increased in delirium even at normal levels of arousal, suggesting that generalized EEG slowing in delirium reflects brain network dysconnectivity beyond the arousal network,[34,35] and that large gaps remain in our knowledge about the neurobiological mechanisms of generalized EEG slowing.

In contrast to the relatively high sensitivity of generalized EEG slowing for delirium, other EEG findings such as triphasic waves were much less sensitive despite being highly specific. Triphasics, other generalized or lateralized periodic discharges, and sporadic discharges were relatively uncommon in our cohort, at a rate similar to those reported in some prior studies.[36] Prior work has suggested that such EEG features may be more reflective of the etiology of delirium or encephalopathy.[37] In contrast, slowing here appeared to reflect the severity of delirium but was less etiologically specific.

Figure 4 EEG slowing and delirium were associated with poor clinical outcomes



Clinical outcomes are shown for patients stratified by delirium status (gray = no delirium, red = delirium) and generalized EEG slowing (lighter shade/− = no EEG slowing; darker shade/+ = with EEG slowing). (A) Both EEG slowing and delirium were associated with increased length of stay (robust rank estimation for linear models/analysis of variance: main effects of EEG slowing $F = 17.9$, $p < 0.001$; and delirium $F = 11.9$, $p < 0.001$; no significant interaction $F = 2.9$, $p = 0.092$). Horizontal black lines depict medians; bars depict interquartile ranges; and thin vertical lines depict ranges (minimum–maximum). Length of stay is plotted on a log scale given the long-tailed distribution. (B) Both EEG slowing and delirium were associated with worse functional outcomes as measured by the Glasgow Outcome Scale (main effects of EEG slowing $F = 7.2$, $p = 0.008$; delirium $F = 8.8$, $p = 0.003$; no significant interaction $F = 0.08$, $p = 0.774$). (C) Rates of mortality differed depending on delirium status and EEG slowing (4-sample test for equality of proportions: $\chi^2 = 14.1$, $p = 0.003$). EEG slowing was associated with increased mortality in patients both with and without delirium (χ^2 and p values reflect post hoc χ^2 tests between the indicated groups).

Generalized EEG slowing has been shown to predict poor clinical outcomes for some specific patient populations such as those with postanoxic coma[38] or patients with sepsis in the ICU,[39] although not patients with encephalitis[40] or general patients in the ICU.[41] Our results demonstrate that generalized EEG slowing can predict poor clinical outcomes in a population with a wider variety of disease and clinical contexts. Given that generalized slowing correlated highly with delirium and that delirium is also associated with poor clinical outcomes,[33] it was surprising that EEG slowing remained associated with poor clinical outcomes even after adjustment for delirium status or severity.

Results were consistent with the use of either the 3D-CAM criteria for delirium or the clinical diagnosis of delirium as per the care teams. Both measures were highly, but not completely, concordant with each other, as well as with EEG slowing. Some of these discrepancies may be due to fluctuations in delirium, particularly when considering severity. Clinical diagnosis of delirium, often with reference to *Diagnostic and Statistical Manual of Disorders* criteria, is currently the most accepted gold standard. Clinical delirium diagnosis does not, however, typically measure delirium severity, and clinicians were not constrained to assess delirium within 1 hour of EEG recording, which may be important for a fluctuating condition. Our data suggest that important prognostic information remains in even a single routine EEG that is not captured by standard clinical assessment of delirium. Future work is necessary to understand whether clinical assessment of delirium and EEG slowing reflect incomplete views of the same process or whether they are each influenced by additional, independent processes.

There are several limitations to our study. EEG referral for altered mental status was initiated by providers; thus, it is unclear to what extent our findings will generalize to patients who do not trigger such an evaluation. Our study was also performed under a waiver of consent, with the advantage of being as inclusive as possible and minimizing some types of selection bias. However, this inclusive design was associated with some limitations in the cognitive evaluations that could be performed. We attempted to exclude patients with documented histories of dementia, who may have different baseline and delirium-related EEG changes,[42–44] but it is possible that we did not fully exclude all patients with dementia who might have been identified only with more detailed collateral

information. It is therefore unclear how these results may generalize to patients with dementia. In addition, each patient was evaluated only once, which precluded investigation of subsequent cognitive outcomes that could not be captured by the GOS, as well as baseline status and fluctuations. Given that a significant proportion of delirium develops after arrival to the hospital,[45] however, baseline EEG measurements may be attainable in future studies in a subset of patients who subsequently may become delirious.

EEGs were analyzed with routine clinical interpretation in a single center, which identified theta or delta slowing as absent or present rather than quantifying the degree of EEG slowing. We focused on standard visual interpretation rather than quantitative analysis given that this type of interpretation is already a routine part of clinical practice in most centers. It is possible that quantitative EEG analysis may provide stronger patient-specific monitoring of delirium severity, but it is notable that even qualitative assessment is so informative.

Our work highlights the prognostic seriousness of routine clinical EEG slowing and suggests that even a single observation of generalized EEG slowing is a significant marker for poor clinical outcomes, even after accounting for the presence or severity of delirium. EEG slowing may therefore be a useful tool to identify higher-risk patients that will allow us to understand commonalities among varying etiologies of delirium, as well as an objective method to monitor clinical course in delirium, including potentially responses to novel therapies.

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