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LETTER TO THE EDITOR

An automated electroencephalography algorithm to detect polymorphic delta activity in acute encephalopathy presenting as postoperative delirium

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Single-channel electroencephalography (EEG) can detect postoperative delirium based on increased relative delta power.[1,2] However, relative delta power can be nonspecific since noise, such as eye movements and glossokinetic artifacts, also manifest predominantly within this low-frequency range. Acute encephalopathy presenting as delirium is characterized in EEG by arrhythmic slow waves known as polymorphic delta activity (PDA).[3–5] To provide a delirium monitoring tool suitable for routine daily care, an algorithm was developed that functions without any manual EEG epoch selection, since this can be time-consuming and has high interoperator variability. The current multicenter study aimed to investigate the detection of acute encephalopathy using automated artifact rejection and predefined wave shape characteristics for PDA. Additionally, we tested its performance as a delirium monitor.

Elderly patients with major surgery underwent single-channel EEG (Fp2-Pz, sampling frequency 512 Hz) in the resting state with eyes closed, directly followed by an extensive delirium assessment to capture the physiological and clinical status of the patient in a time frame that is unlikely to be subject to fluctuations. The study protocol is described elsewhere[2] and in Supplement 1 of Appendix S1. Detection of PDA was performed with a fully automated algorithm that took about a minute to run five modules: (i) a preprocessing module; (ii) an artifact module; (iii) an eye movement module (since eye movements are challenging to distinguish from PDA in Fp2-Pz); (iv) a module to detect PDA wave shapes in the first nonrejected 96 seconds; and (v) translation to a likelihood score (1–5). Examples and outcomes are shown in Fig. 1 and algorithm details are described in Supplement 2 of Appendix S1.

PDA detection was first compared with acute encephalopathy classifications of three experienced, well-trained EEG experts and secondly with delirium classifications of two (or three, in case of discordance) experienced clinicians who based their diagnosis on at least 20 minutes of video-recorded and standardized cognitive testing. Details regarding the expert panels are described in Supplements 3 and 4 of Appendix S1. Reference panels must consist of more than one expert, as we previously showed that experts often

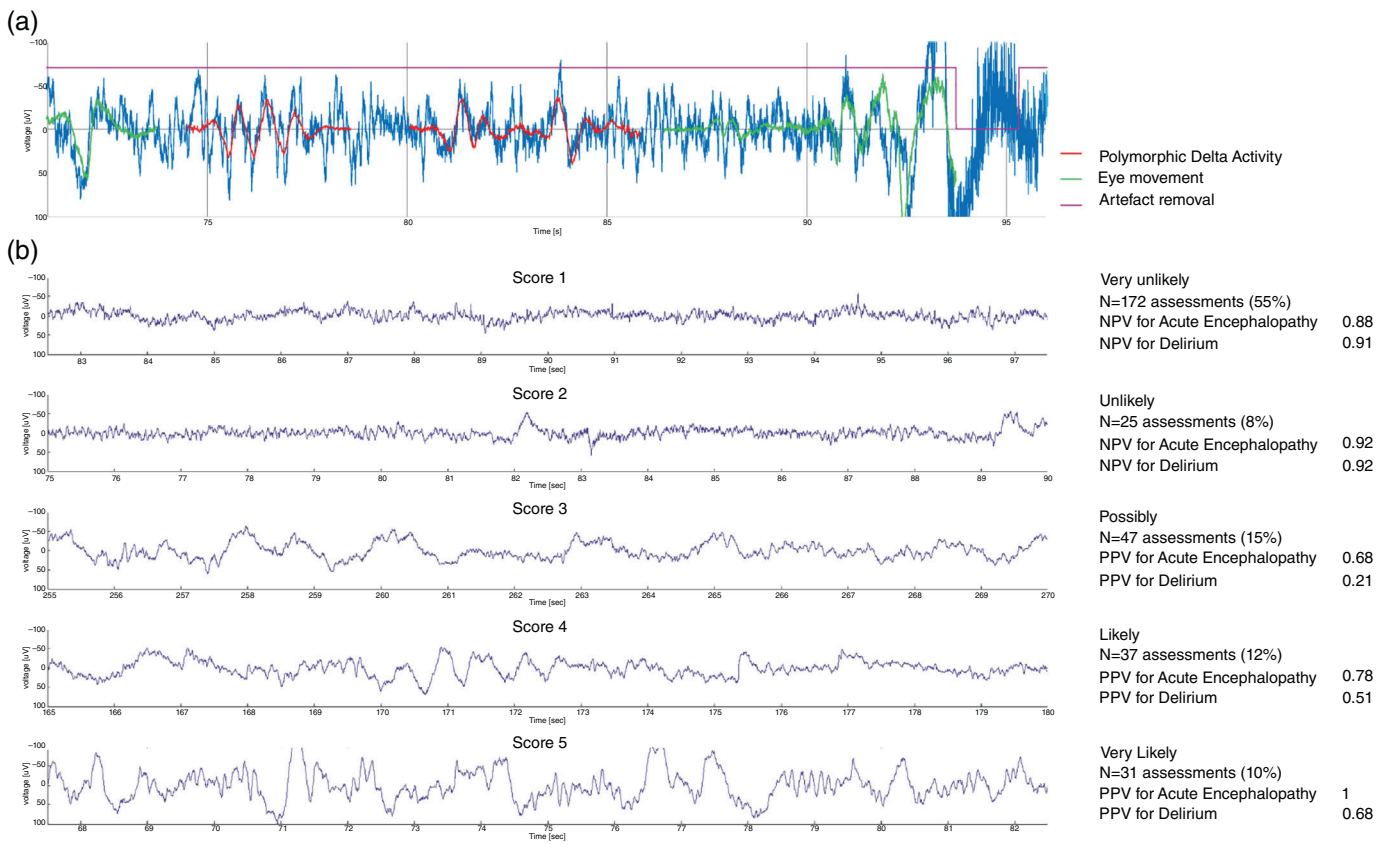

Fig. 1 Examples of detected wave shapes and the polymorphic delta activity (PDA) score. (a) Examples of detected wave shapes including PDA (red) and eye movement (green). The pink line represents the artifact algorithm that deselects improper electroencephalography signal. (b) Five groups were distinguished, representing the likelihood of delirium based on the amount of detected PDA. Within this range, scores 1 and 2 represent 'no acute encephalopathy' and scores 3 to 5 represent 'acute encephalopathy.' This cutoff showed a sensitivity of 0.80 and a specificity of 0.88 for acute encephalopathy. Sensitivity and specificity for delirium, using the same cutoff, were 0.74 and 0.73, respectively.

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disagree on the diagnosis of delirium although they based their conclusion on exactly the same clinical information.[6]

The 145 included patients were assessed on the first three postoperative days (n = 321 assessments), of which the artifact algorithm rejected nine assessments (success rate 97%; see Supplement 5 of Appendix S1 for statistics, Supplement 6 of Appendix S1 for participant flowchart, and Supplement 7 of Appendix S1 for characteristics). No patients were classified as delirious on the day before surgery (T-1) by the clinical experts.

PDA detection achieved an area under the curve of 0.86 (95% confidence interval, 0.81–0.90) for acute encephalopathy and 0.78 (95% confidence interval, 0.71–0.85) for delirium (see Supplement 8 of Appendix S1 for figures). PDA detection correlated with the likelihood of delirium, its severity, and the levels of attention and consciousness (all $P < 0.001$, Supplement 9 of Appendix S1) Fig. 1 shows predictive values for acute encephalopathy and delirium for various PDA scores.

These results are comparable with previous minimal-lead EEG studies.[2,7–9] However, those studies required manual involvement instead of using a predefined 2-minute self-functioning algorithm, which is essential for application in routine daily care. In addtion, previous studies made a model based on feature selection of their testing cohort, while we validated a prespecified type of EEG activity (i.e. PDA) based on knowledge derived from literature[4] for reproducibility purposes.

Interestingly, we found that the EEG experts included more positive assessments (i.e. acute encephalopathy: 47% [68 patients]; 115 assessments) than the clinical experts (delirium: 32% [47 patients]; 68 assessments). The overlap between both expert panels was 70% (see Supplement 10 of Appendix S1 for an overview of the classifications). Previously, we showed that acute encephalopathy without delirium is associated with a significantly higher Delirium Rating Scale-Revised-98 (DRS-R-98) score than no acute encephalopathy and no delirium.[5] We speculate that acute encephalopathy without delirium indicates subsyndromal delirium with the potential to deteriorate to delirium. PDA may therefore be an early indicator of delirium, which might allow timely treatment.

The use of two electrodes in a frontal–parietal derivation was based on an explorative study[1]; however, there is a lack of concordance in the best channel localization.[7–9] Our proper screening of patients makes it unlikely, although not impossible, that any present PDA could be attributable to other causes such as an unknown structural cerebral abnormality.[10] However, stratified analysis on the presence or absence of a previous stroke or transient ischemic attack yielded similar results (Supplement 11 of Appendix S1). PDA caused by sleep seems unlikely since the researcher constantly ensured that patients were awake.

In conclusion, our findings show that automated detection of PDA can identify acute encephalopathy clinically presenting as delirium. PDA detection can be implemented in daily clinical care since the output is generated without any manual interference after recording.

Acknowledgments

The authors would like to especially thank the Dutch delirium study group who served as members of the clinical expert panel, as well as Nizare R.V.R. Henriquez and Nico W. Teunissen of the Department of Neurology and Neurosurgery and University Medical Center Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, who served as members of the EEG expert panel.

Disclosure statement

Arjen J.C. Slooter is a nonsalaried advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any (future) profits from EEG-based delirium monitoring will be used for future scientific research only. Frans S.S. Leijten is also a nonsalaried advisor and holds shares in Prolira. None of the other authors report any conflicts of interest. The sponsor and Prolira had no role in the study design, data analysis, data interpretation, or the decision to submit for publication.

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Clinical trial information

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Supporting information

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Supplement 1 Detailed study protocol

The current investigation is based on data from a prior prospective, multicentre cohort study, described in more detail elsewhere.[1] The study design was approved prior to patient enrolment by the local ethical committee of University Medical Center Utrecht (protocol 13-634) and registered at clinical trial (NCT02404181, principal investigator: AJC Slooter). This manuscript adheres to the applicable Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines. All patients gave signed informed consent and anonymity was preserved. Elderly patients were included who were ≥ 60 years, scheduled for major surgery with an expected hospital stay of ≥ 2 days, and considered at risk of delirium.[2] Exclusion criteria were neurosurgery and the inability to undergo cognitive testing due to deafness or a language barrier. Additionally, we excluded patients with a Mini-Mental State Examination (MMSE) ≤ 23 because dementia could affect slow-wave EEG activity.[3,4] All measurements were performed by a trained researcher on the day before surgery (T-1) and during each of the first three postoperative days (T1-T3).

Supplement 2 Detection of polymorphic delta activity (PDA)

Patients underwent EEG recordings in resting state with eyes closed. All measurements were performed by a trained researcher on the day before surgery (T-1) and during each of the first three postoperative days (T1-T3). The researcher constantly ensured patients were awake and sat still while recording. EEG measurements were directly followed by an extensive standardized delirium assessment by a trained researcher.

EEG's (Fp2-Pz and T8-Pz. using Fpz as a reference) were originally recorded using a MobiMini-system (TMSi. Oldenzaal. the Netherlands).[1] Detection of PDA was performed with a fully automated wave shape analysis algorithm (DeltaScan algorithm version 2.4.2). An SEEG 100 WhaleTeg system was used to re-play Mobi-Mini data and record solely Fp2-Pz (sampling frequency 512Hz) as if data was recorded with the latest device: a DeltaScan monitor.

The algorithm consists of 1) a pre-processing module, 2) an artefact module and 3) a module to detect PDA wave shapes. The first pre-processing step was to use a high-pass filter (cut-off 0.125Hz) to remove low-frequency noise and slow drift from the EEG recordings. Secondly, multiple filters were used to remove line noise from power grids (50/60), device disturbances (24/64 Hz) and their harmonics. After pre-processing, the artefact module ran to reject non-EEG signals such as motion artefacts, disconnected electrodes or strong electrical interference.

Detection of PDA was run on the first non-rejected 96 seconds using a classifier based on supervised machine learning techniques. The classifier was trained to recognise wave

characteristics of PDA on a training dataset that contained surgical patients with delirium (n=28) or without delirium (n=28).[5] Training data of healthy volunteers (n=27) was added to provide target-free EEG to distinguish PDA from delta activity generated by eye movements. Both types of wave shapes were manually marked by a clinical technician with 10 years of experience in neurophysiology. Examples of these detected wave shapes and the artefact module are shown in figure 1.

Thereafter, the amount of detected PDA was translated to an ordinal score ranging from 1 to 5 (Figure 1B). This PDA score aims to represent the likelihood of acute encephalopathy labelled: "1" very unlikely, "2" unlikely, "3" possibly, "4" likely and "5" very likely. Within this range, scores 1 and 2 are intended to represent "no acute encephalopathy" and scores 3-5 "acute encephalopathy".

PDA scores were set on the prespecified Receiver Operating Characteristic-curve (ROC) of our sample that was completely independent of the training dataset. A PDA score of "1" was assigned when none or only one specific PDA wave was detected in the whole EEG recording. Since the boundary between PDA scores 2 and 3 is crucial for assignment to the categories "no acute encephalopathy" and "acute encephalopathy an optimum was chosen between the sensitivity, specificity and negative predictive value (NPV) using the classification of EEG experts and the clinical experts described above. The boundaries between PDA scores 3, 4 and 5, were set by sorting the positively assessed EEG measurements based on the amount of detected PDA and dividing them into three equal bins. Examples of recordings with PDA scores (1-5) are shown in figure 1B.

Supplement 3 Assessment of acute encephalopathy by EEG experts

The reference for acute encephalopathy assessment consisted of the classification of three EEG experts from the Department of Clinical Neurophysiology at the University Medical Center Utrecht, the Netherlands who visually inspected the single-channel EEGs, independently of each other and blinded to all clinical information. All experts had over 15 years of clinical EEG experience. To provide training in recognising delta waves and artefacts such as eye movement, a training dataset was used,[5] which contained of 21-channel EEGs (n=56) paired with their Fp2-Pz EEG derivation. PDA was defined when four criteria were met: 1) a frequency within 0.5 to 5 Hz; 2) being present at least three times per minute; 3) containing at least two sequent waves; 4) having a higher amplitude than alpha activity in the same recording. Blinded to clinical information, the EEG experts classified the single-channel EEGs into either "acute encephalopathy", "no acute encephalopathy" or "possible acute encephalopathy/doubt" in case of a measurement with many artefacts, when there was uncertainty about eye movements or measurements with only a few polymorphic delta waves.

To provide a final binary conclusion "no acute encephalopathy" or "acute encephalopathy", discussion sessions were organised to evaluate the EEGs for which there was no majority vote or when the majority vote conclusion was "doubt".

Supplement 4 Assessment of delirium by clinical experts

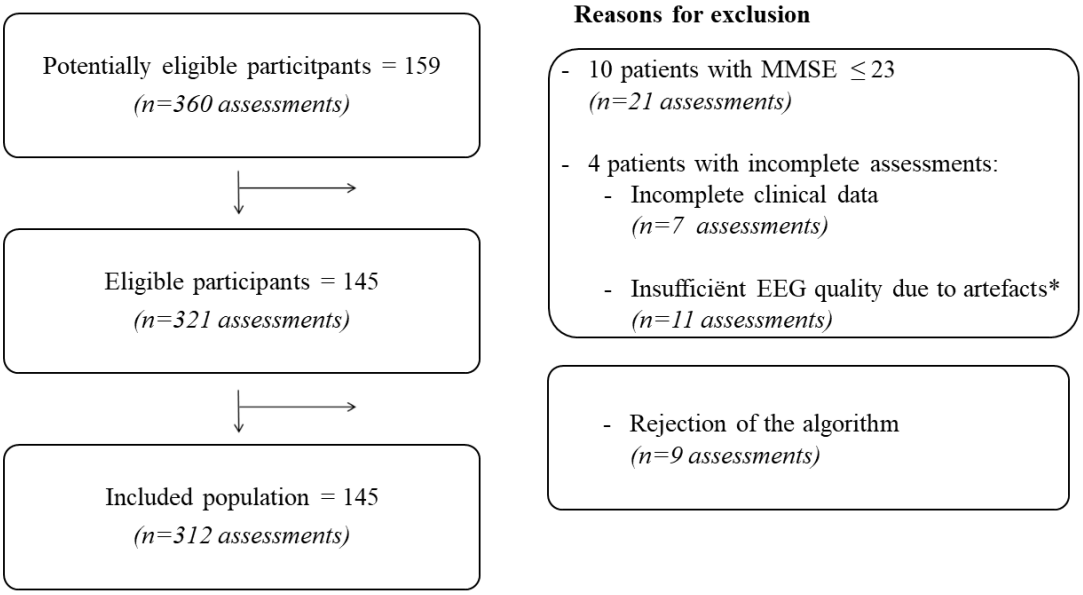
Delirium assessments were performed by trained researcher based on a standardised, videotaped cognitive assessment of about fifteen minutes that included the Delirium Rating Scale Revised-98 (DRS-R-98),[6,7] the Richmond Agitation and Sedation Scale (RASS),[8] and the Confusion Assessment Method in the ICU (CAM-ICU).[8,9] These videotapes were rated by varying pairs of two, or in case of disagreement three, delirium experts. The complete panel contained 38 clinicians, mainly psychiatrist and geriatricians, with at least five, but mostly over 10 years of experience. Blinded to each other and the EEG recording, they classified patients as either having "no delirium", "possible delirium/subsyndromal delirium" or "delirium", according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) delirium criteria. In addition, the clinical experts reported the likelihood of delirium on a numeric rating scale (NRS) ranging from 1 to 10 (higher scores represented a higher likelihood of delirium). The final classification was based on the majority vote, where "possible delirium" was grouped with "delirium."

Supplement 5 Statistical analyses

First, we compared positive assessments for acute encephalopathy as classified by PDA detection (PDA score 3-5) with the final classification of acute encephalopathy according to the EEG experts. Secondly, we compared the positive assessments according to PDA detection with the final diagnoses of delirium according to the clinical experts, detailed earlier. Next, we expressed the performance of PDA detection as two Receiver Operating Characteristic (ROC) for the two different expert panels presenting the sensitivity and specificity per PDA score ranging from 1-5. In addition, we performed a stratified analysis based on the presence or absence of a medical history of stroke or either transient ischemic attack (TIA) and compared strata with DeLong's test.

Predictive values were calculated for each PDA score boundary ranging from 1-5 (Figure 1B) using the group total of that specific score as denominator. Spearman's rank correlation coefficients (rs) were determined to investigate correlations between PDA Scores (1-5) and the scores of the clinical experts on likelihood of delirium (averaged Numeric Rating Scale, NRS), the severity of delirium (averaged DRS-R-98), level of attention (i.e., averaged item-10 of the DRS-R-98 score), and level of consciousness (averaged RASS). A P-value of < 0.05 was considered statistically significant. Analyses were performed with SPSS version 26.0.0.1 and Ri386 version 4.0.3.

Supplement 6 Flowchart of included patients and assessments



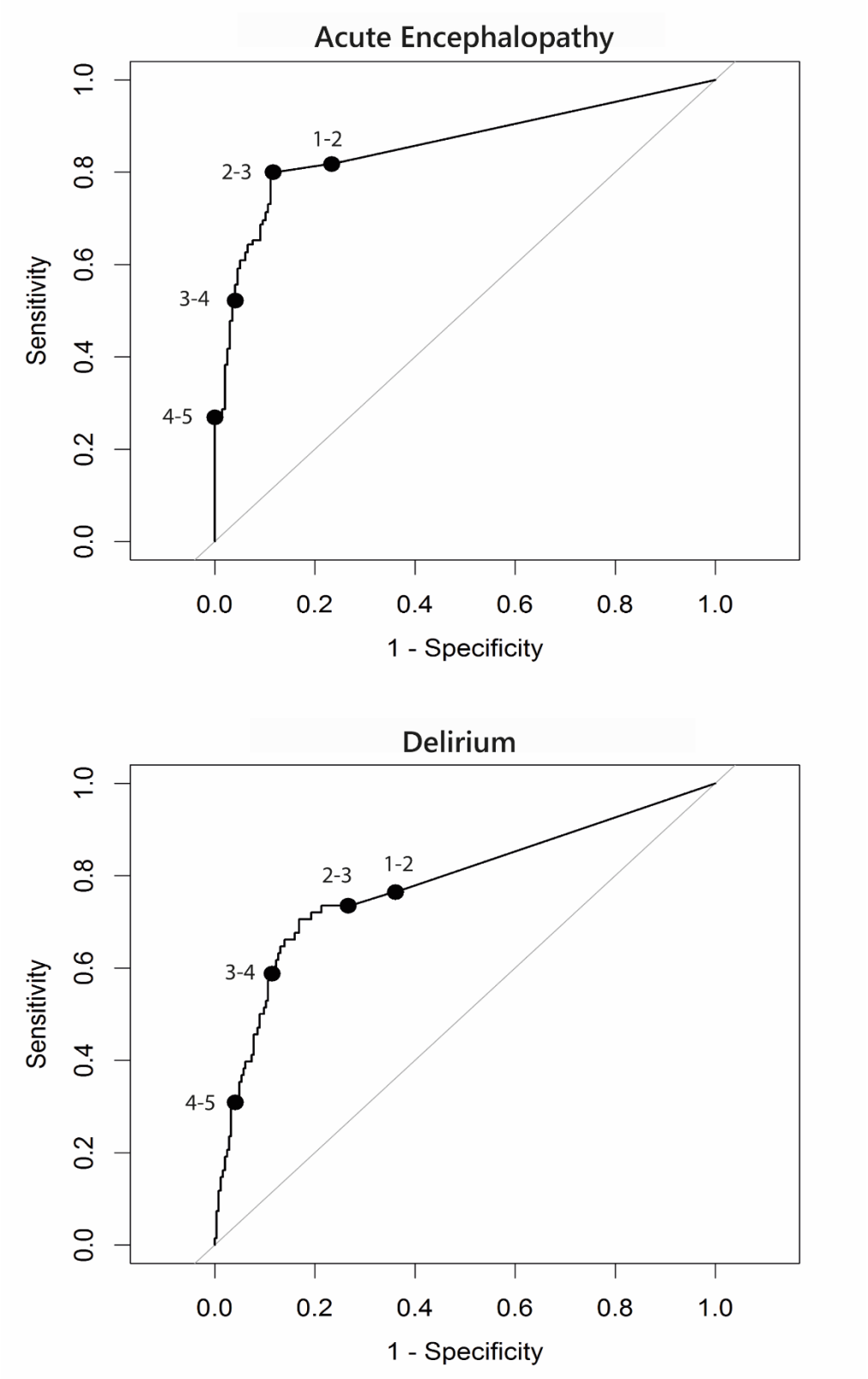
**EEG's with insufficient quality were selected to be so by the EEG experts (n=11 assessments). Of the remaining 145 patients (n=321 assessments), the automated artefact algorithm rejected 9 assessments (success rate 97%).*

Supplement 7 Patient characteristics

	All patients (n=145)
Age in years, mean (SD)	77 (6.3)
Male sex, n (%)	99 (68%)
Female sex, n (%)	46 (32%)
MMSE[†], median (IQR)	28 (27-29)
Medical history, n (%)	
Stroke or TIA[‡]	40 (29%)
Any psychiatric disease[§]	6 (4%)
>10 IE alcohol/week	29 (25%)
Alcohol IE/week, median (IQR)	2 (12)
Benzodiazepine use <24h	25 (17%)
Surgery type, n (%)	
Cardiothoracic or vascular	131 (90%)
Orthopaedic	8 (6%)
Other	6 (4%)

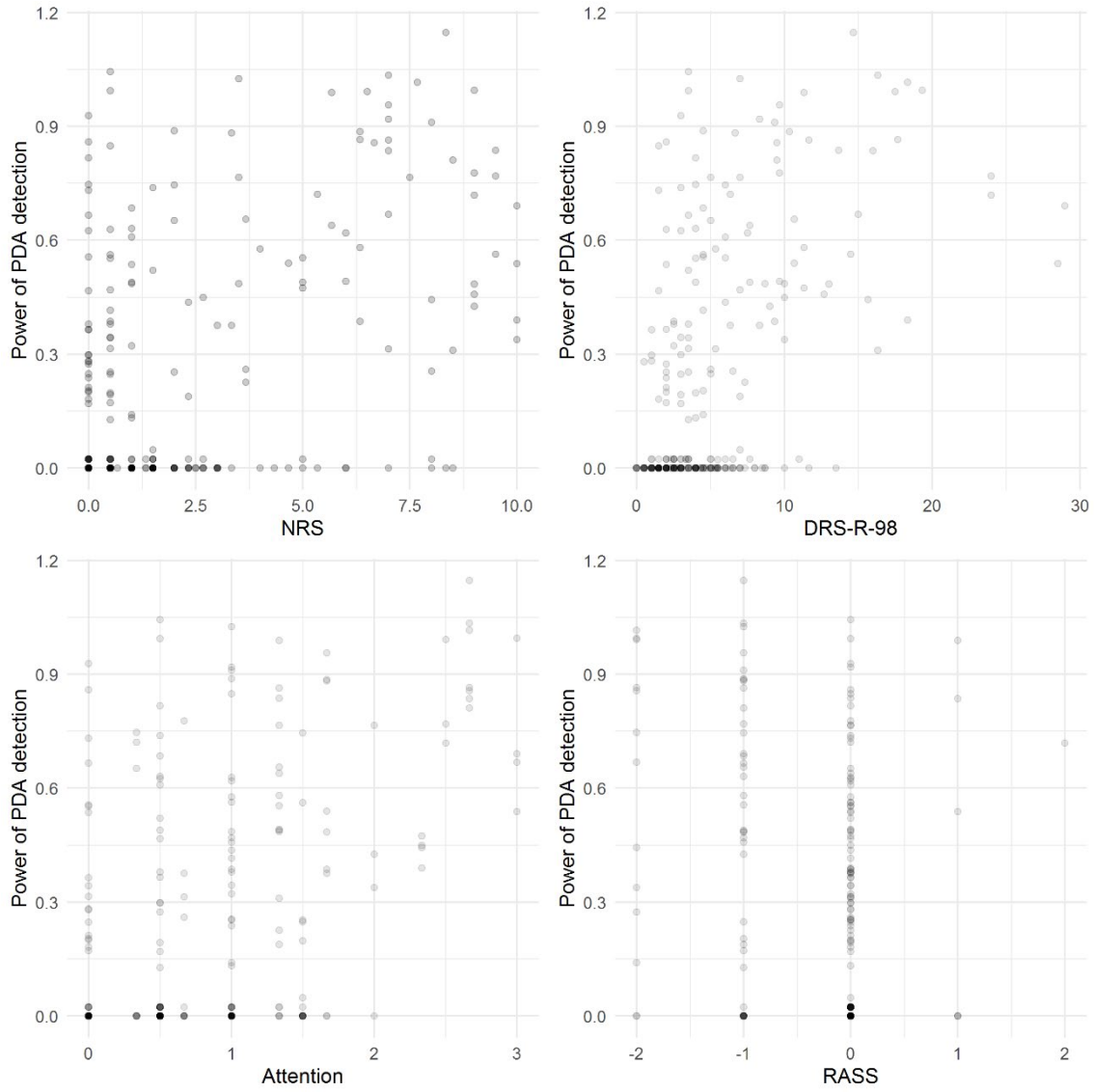
Data are presented as mean with standard deviation (SD), median with interquartile range (IQR), or number (n) with percentage (%). [†]Mini-Mental State Exam, [‡]Transient ischemic attack, [§]All patients with a psychiatric disease had a medical history of depression. One patient had a medical history of bipolar disorder.

Supplement 8 Receiver Operating Characteristic (ROC) curves for Polymorphic Delta Activity (PDA)



ROC-curves for Acute Encephalopathy and Delirium show the sensitivity and 1-specificity for every boundary of the PDA Score (See figure 1 for a detailed explanation of the PDA score). The Area Under the Receiver Operating Characteristic (AUC) for acute encephalopathy was 0.86 (95% Confidence Interval (CI) 0.81-0.90) using the classification of the EEG expert panel as a reference. The AUC for delirium was 0.78 (95% CI 0.71-0.85) using the classification of the clinical expert panels as a reference.

Supplement 9 Scatterplots of power of PDA detection in relation to NRS, DRS-R-98, Attention and RASS score



Power of PDA detection was log- transformed (log10(power+1)) on the y-axis. PDA detection correlated significantly with the likelihood of delirium (NRS. rs= 0.37, 95%CI 0.25-0.47), the severity of delirium (DRS-R-98. rs= 0.46, 95%CI 0.36-0.55), the level of attention (i.e. item-10 of the DRS-R-98 score. rs= 0.41, 95%CI 0.32-0.51) and level of consciousness (RASS. r_s= -0.32, 95%CI -0.44- -0.19) (p< 0.001 for all comparisons).

Supplement 10 Contingency table of Polymorphic delta activity (PDA) score and assessments by the expert panels

PDA	DRS-98-R	RASS	Acute encephalopathy		Delirium			Total
Score	Median (IQR)	Median (IQR)	-	+	-	+ (hypo/mixed/hyper)		
1	2.5 (1.1 - 3.9)	0 (0 - 0)	151	21	156	16	(6 / 4 / 6)	**172**
2	3.0 (1.7 - 4.3)	0 (0 - 0)	23	2	23	2	(0 / 1 / 1)	**25**
3	3.5 (1.4 - 5.6)	0 (0 - 0)	15	32	37	10	(1 / 0 / 9)	**47**
4	6.3 (3.0 - 9.7)	0 (-0.5 - 0.5)	8	29	18	19	(2 / 4 / 13)	**37**
5	9.5 (4.8 - 14.2)	-1 (-1.5 - 0.5)	0	31	10	21	(11 / 1 / 9)	**31**
Total	**3.5 (1.5 - 5.5)**	**0 (0 - 0)**	**197**	**115**	**244**	**68**	**(20 / 10 / 38)**	**312**

Acute encephalopathy -/+ refers to the classification of the panel of EEG experts.

Delirium -/+ refers to the diagnosis of the panel of clinical experts.

Supplement 11 Stratified analysis for a medical history containing TIA or Stroke

	AUC Acute Encephalopathy	AUC Delirium
Patients with a medical history containing TIA or stroke (N=71)	0.81 (0.71-0.91)	0.82 (0.71-0.93)
Patients without a medical history containing TIA or stroke (N=213)	0.90 (0.85-0.91)	0.76 (0.68-0.85)
P-value	0.13	0.42

Supplement 12 Details of authors' contribution

All authors confirmed they have contributed to the intellectual content of this article and gave final approval of the version to be published.

Fienke L Ditzel: this author contributed with data preparation, analysis and preparation of the manuscript

Suzanne CA Hut: this author contributed with data preparation, analysis and revision of the manuscript

Sandra MA Dijkstra-Kersten: this author contributed with data preparation and analysis

Tianne Numan: this author contributed with data collection, data preparation, revision of the manuscript

Frans SS Leijten: this author contributed with data collection and revision of the manuscript

Mark van den Boogaard: this author contributed with data collection and revision of the manuscript

Arjen JC Slooter: this author contributed with data collection and revision of the manuscript

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