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Regular Research Article

DeltaScan for the Assessment of Acute Encephalopathy and Delirium in ICU and non-ICU Patients, a Prospective Cross-Sectional Multicenter Validation Study

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DeltaScan validation

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ABSTRACT

Objectives: To measure the diagnostic accuracy of DeltaScan: a portable real-time brain state monitor for identifying delirium, a manifestation of acute encephalopathy (AE) detectable by polymorphic delta activity (PDA) in single-channel electroencephalograms (EEGs). **Design:** Prospective cross-sectional study. **Setting:** Six Intensive Care Units (ICU's) and 17 non-ICU departments, including a psychiatric department across 10 Dutch hospitals. **Participants:** 494 patients, median age 75 (IQR:64-87), 53% male, 46% in ICUs, 29% delirious. **Measurements:** DeltaScan recorded 4-minute EEGs, using an algorithm to select the first 96 seconds of artifact-free data for PDA detection. This algorithm was trained and calibrated on two independent datasets. **Methods:** Initial validation of the algorithm for AE involved comparing its output with an expert EEG panel's visual inspection. The primary objective was to assess DeltaScan's accuracy in identifying delirium against a delirium expert panel's consensus. **Results:** DeltaScan had a 99% success rate, rejecting 6 of the 494 EEG's due to artifacts. Performance showed an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.86 (95% CI: 0.83-0.90) for AE (sensitivity: 0.75, 95%CI=0.68-0.81, specificity: 0.87 95%CI=0.83-0.91. The AUC was 0.71 for delirium (95%CI=0.66-0.75, sensitivity: 0.61 95%CI=0.52-0.69, specificity: 72, 95%CI=0.67-0.77). Our validation aim was an NPV for delirium above 0.80 which proved to be 0.82 (95%CI: 0.77-0.86). Among 84 non-delirious psychiatric patients, DeltaScan differentiated delirium from other disorders with a 94% (95%CI: 87-98%) specificity. **Conclusions:** DeltaScan can diagnose AE at bedside and shows a clear relationship with clinical delirium. Further research is required to explore its role in predicting delirium-related outcomes. (Am J Geriatr Psychiatry 2023; ■■■:■■■-■■■)

Highlights

- **What is the primary question addressed by this study?**

What is the accuracy of DeltaScan; a portable brain state monitor that offers real-time automated artifact rejection and analysis, delivering a probability score for both acute encephalopathy and delirium in both ICU and non-ICU patients?

- **What is the main finding of this study?**

The device can detect acute encephalopathy and delirium with good discrimination statistics especially in older patients, regardless of their postoperative state, psycho-active medication use, or prior psychiatric history.

- **What is the meaning of the finding?**

The study suggests that the DeltaScan could be a valuable tool for improving delirium monitoring practices, given that delirium is often overlooked, difficult to differentiate from other psychiatric disorders, and current questionnaire-based monitoring tools suffer from inter-rater variability.

OBJECTIVE

Delirium is a prevalent condition in various hospital settings¹ and is associated with prolonged hospitalization,² long-lasting changes in the functional brain network³ grey matter brain volume loss,⁴ and long-term cognitive decline.⁵ Early identification of delirium is critical to treat underlying conditions and prevent these negative outcomes.⁶ Despite the development of several clinical delirium assessment tools⁷ delirium is still commonly overlooked.^{8,9} This may be attributed to the subjectivity of these tools, making it challenging to minimize interrater variability among numerous nurses in daily care.^{10,11} Furthermore, some acute psychiatric disorders can resemble the clinical phenotype of delirium closely, which may lead to false-positive results if delirium assessment tools are used.¹² An objective and reliable device is therefore needed to improve daily delirium detection.

The well-known phenomena of EEG slowing during delirium could function as a potential detection tool,¹³ since EEG slowing correlates with delirium severity^{14,15} and normalizes after delirium resolves.¹⁶ As the slowing is generalized over the entire brain,^{17,18} delirium detection can be done with using only one EEG channel. Fp2-Pz was identified as most suitable channel, because of its application ease and the proven superior sensitivity of the frontal-parietal derivation,¹⁹ whereafter it was independently validated.²⁰ To ensure precision, a pattern more specific than slow wave activity (1–6 Hz) was needed since eye- and glosso-kinetic movement also manifest in EEG activity within this frequency range.

Polymorphic delta activity (PDA) is a slow EEG pattern typical for delirium.¹⁸ Recently, a panel of EEG experts defined acute encephalopathy (AE) based on prespecified characteristics of PDA within single-channel EEG, and three-quarters of their final diagnoses overlapped with the clinical diagnoses of delirium.²¹ A fully self-functioning algorithm was trained to detect and reject artifacts, and subsequently sum the number of PDA to calibrate it on a likelihood score ranging from 1 to 5, which correlates with the probability of delirium, its severity, and the levels of attention and consciousness as determined by delirium experts (all $p < 0.001$).²² However, these studies solely measured delirium in an older postoperative non-ICU population using single electrodes that

needed several minutes to be carefully placed by trained hands. To improve feasibility, a portable easy-to-use brain state monitor with real-time automated analysis (DeltaScan) was developed.

The current study aimed to validate DeltaScan, including its monitor, electrode patches and algorithm in ICU and non-ICU patients. First we validated the device for AE, the pathobiological brain process underlying delirium,^{23,24} by comparing the self-functioning algorithm with visual inspection of EEG by experts. Thereafter we were interested in the translation of these EEG changes to symptoms; Our primary aim was to assess DeltaScan's diagnostic test accuracy (AUROC) as a delirium detector by comparing its outcome with a majority vote of three delirium-experts. As acute psychiatric disorders can resemble the clinical phenotype of delirium closely, we recognized the device's potential contribution considering differentiating delirium from other psychiatric conditions. For the last aim we investigated the number of false positives in an additional group of hospitalized patients with a psychiatric disorder.

METHODS

Study Design, Setting, and Study Population

This was a prospective, cross-sectional, multicenter validation study in ICU and non-ICU patients. Data was collected between 2019 and 2021 in the following ten Dutch hospitals: University Medical Center (UMC) Utrecht, Diaconessenhuis Utrecht, Radboudumc, Isala Zwolle, Isala Meppel, Tergooi Medical Center, Franciscus Gasthuis & Vlietland, Onze Lieve Vrouwe Gasthuis, Amphia, Medisch Spectrum Twente. Patients were included when admitted on the days that the researchers visited the hospital. Inclusion criteria for the ICU sample was an expected ICU stay of at least 24 hours and a minimum age of 18 years. Patients admitted to a non-ICU department were included if they had an expected stay of at least 48 hours and a minimum age of 60. Exclusion criteria for both ICU and non-ICU patients were post-cardiac arrest, brain surgery or any type of brain injury within the previous 6 weeks; admission for a primary neurological or neurosurgical condition; known dementia; use of lithium; presence of an intracranial metal plate or device; a language barrier or deafness;

DeltaScan validation

or a Richmond Agitation-Sedation Scale (RASS) score below -2. Patients with severe agitation disturbing the EEG measurement were also excluded. The third study sample included adult (18+) patients with an acute psychiatric disorder admitted to the department of psychiatry of UMC Utrecht, using the same in- and exclusion criteria described above.

DeltaScan Measurements

In brief, a DeltaScan measurement was at first compared to visual inspection of the EEG by experts to see if it was correct in diagnosing AE. The next step was to access the resemblance between AE and its expression in clinical delirium symptoms. Our primary analysis was to compare DeltaScan's performance as a delirium detector. The AE and delirium reference are described in detail below. The 4-minute DeltaScan measurement included a resting-state EEG with eyes closed, using a self-adhesive patch with one reference electrode at Fpz and two measurement electrodes at Fp2 and Pz, according to the 10–20 system for location of EEG electrodes. In a small sub cohort of 15 patients we measured reproducibility by performing 3 measurements straight after each other (in 12 minutes total). The DeltaScan score was calculated as explained in detail elsewhere,²² within 1 minute using DeltaScan algorithm 2.4.2. Shortly, the DeltaScan algorithm consisted of four modules: (1) preprocessing; (2) automated artifact (including eye movements) detection and rejection; (3) detection of PDA wave shapes in the first 96 seconds; and (4) translation to a scale from 1 to 5, which can be interpreted as the likelihood of underlying AE and delirium. Scores 1–2 are interpreted as indicating the absence of AE and delirium, scores 3–5 indicating their presence.²² The researcher, the patient, and both EEG and delirium reference panels were blinded to the DeltaScan scores.

**Acute Encephalopathy Reference as Defined by
Visual Inspection of the EEG Trough
Neurophysiologists**

All EEG recordings were visually inspected by three EEG experts, each with more than 16 years' experience with clinical EEG. The experts used, independently of each other and blinded to the other measurements, the following criteria for AE: (1) polymorphic delta waves should have higher amplitudes

than alpha waves; (2) the frequency of polymorphic delta waves should lie within 0.5–5 Hz; (3) polymorphic delta should have a presence of at least 2 subsequent waves (4) these runs should be present at least three times per minute.²¹ The final classification AE was based on the majority vote of the three EEG experts.

**Delirium Reference as Defined by Clinical
Delirium Experts**

A trained researcher performed the 10-minute Delirium Interview²⁵ just prior to the DeltaScan measurement and compiled the results together with observations and information from the electronic health record (EHR) 24 hours before and 12 hours after the measurement. This application of the Delirium Interview has a sensitivity of 89% (95% confidence interval (CI): 72%–98%) and a specificity of 82% (95% CI = 71%–90%),²⁵ and targets the DSM-5²⁶ criteria by combining several delirium detection tools (The 4 A's test,²⁷ The Confusion Assessment Method (CAM),²⁸ Cognitive Test for Delirium,²⁹ Delirium Rating Scale Revised 98 (DSR-R98),³⁰ Delirium observation screening scale (DOSS)³¹ and the Intensive Care Delirium Screening Checklist (ICDSC)).³² All collected information was sent out to three experts. (Supplement 1 represents an illustrative case). The three delirium experts provided, independently of each other and blinded to the other measurements, each delirium interview with the diagnosis "delirium" or "no delirium," and assigned a delirium probability score ranging from 1 (certainly no delirium) to 10 (certainly delirium). The panel of experts comprised 17 clinicians, primarily geriatricians and psychiatrists, who had an average of 17 years of clinical experience (standard deviation 6.3 years). Each of these clinicians encountered approximately 10 delirious patients weekly. The final classification of delirium was based on the majority vote of the three experts, while the final probability score was the average of the three scores of the experts.

Statistical Analysis

In this study, sample size calculation was based on the Negative Predictive Value (NPV) for delirium within the ICU and the non-ICU population conform Buderer et al.³³ We aimed for a high NPV as a

subsequent step in the management of patients with a positive DeltaScan will most likely be further diagnostic testing, which is clinically considered to have a lower risk compared to missing acute encephalopathy/delirium. We aimed to achieve an NPV of 0.8, requiring a total study population with a minimum of 399 and a maximum of 668 measurements based on a delirium prevalence between 10% and 50%. More details regarding the sample size calculation can be found in [Supplement 2](#).

In our primary analysis, we compared the number of detected PDA according to algorithm version 2.4.2 with the final classifications of either AE or delirium using a Receiver Operating Characteristic curve (ROC). Sensitivity and specificity were plotted for each DeltaScan score. Positive Predictive Value (PPV) and NPV's were calculated using only positive (DeltaScan score 3–5) and negative results (DeltaScan score 1–2). Reproducibility of 3 DeltaScan scores measured directly after each other were analyzed with the two-way random single score intraclass correlation (C,1). Positive and negative outcome were compared for the three measurements with Fleiss' Kappa.

Thereafter, we performed stratified analyses on ICU versus non-ICU patients, patients aged at least 60 years or an age below 60 years, patients with or without preceding surgery, and with or without relevant psycho-active medication administered within the last 24 hours. This medication was a priori defined and performed only when after study completion was found that at least 10% of the cohort used this medication. AUCs were compared between strata with the DeLong's test. A Spearman correlation (r_s) was used to study the association between the DeltaScan score and the mean delirium probability scored by the three delirium experts.

Analyses were performed with SPSS version 26.0.0.1 and R version 4.0.3. Data distribution was assessed by visually inspecting histograms, boxplots and QQplots. The p-values below 0.05 were considered statistically significant.

RESULTS

Characteristics of the Study Population

Of the 660 participants that were eligible for the study, 494 (75%) were included for data analysis

([Fig. 1](#): Participant flowchart). DeltaScan rejected 6 of those EEGs (success rate 99%). The final study population included 488 patients with a median age of 75 years (IQR: 64–87), 53% were male and 29% delirious. ([Table 1](#) characteristics).

Overall Performance of DeltaScan

The AUC for AE was 0.86 (95% confidence interval [CI]: 0.83–0.90) and 0.71 (95% CI = 0.66–0.75) for delirium versus no delirium ([Fig. 2](#)). We aimed for a NPV of 0.80 which turned out to be 0.82 (95% CI = 0.77–0.86). The DeltaScan detected AE with a sensitivity of 75% (95% CI = 68%–81%) and specificity of 87% (95% CI = 83%–91%). For delirium, sensitivity and specificity were 61% (95% CI = 52%–69%) and 72% (95% CI = 67%–77%, [Fig. 2](#)). When evaluating reproducibility an intraclass correlation of 0.82 (95% CI = 0.62–0.93, N = 15) was obtained. Instability was observed solely in delirious patients (frequency 10/15 = 67%), while complete stability of 100% was noted in nondelirious patients ([Supplement 3](#)).

Subgroup Performance of DeltaScan

The AUC of AE was 0.88 (95% CI = 0.84–0.93) for the ICU and 0.84 (95% CI = 0.79–0.89) for the non-ICU department ($p = 0.262$). The AUC for delirium was 0.66 (95% CI = 0.59–0.73) for the ICU and 0.73 (95% CI = 0.65–0.81) for the non-ICU department respectively ($p = 0.206$, [Fig. 2](#)). DeltaScan performance did not differ for postoperative delirium versus non-postoperative or whether patients used benzodiazepines, opioids, or antipsychotics within the last 24 hours preceding the measurements ([Supplementary Table 4](#) for data on users of a group of psycho-active medication). The AUC for delirium was higher in patients aged at least 60 years (AUC = 0.73, 95% CI = 0.68–0.78, N = 432) compared to patients younger than 60 years (AUC = 0.56, 95% CI = 0.40–0.72, N = 57, $p = 0.049$, [Supplementary Table 5](#)). Both sensitivity 0.55 (95% CI = 0.32–0.77) as the specificity 0.56 (95% CI = 0.38–0.72) were lower in younger patients. Stratified analysis for age using AE as reference gave comparable performances. (≥ 60 years: AUC = 0.90, 95% CI = 0.82–0.90, Age < 60 years: AUC = 0.86, 95% CI = 0.81–0.98)

DeltaScan validation

FIGURE 1. Participant flowchart. In total, 5% (N = 31) of the patients were excluded because not all the required data were available. During demographic data extraction, we excluded 53 patients (9%) because they did not meet all inclusion criteria on closer inspection. Another 73 patients (13%) were excluded because of Electromagnetic compatibility (EMC) disturbance in the EEG, a hardware problem that was resolved within the first year of enrolment. A total of 18 (3%) patients were excluded because of poor EEG quality based on visual inspection that could not be provided with an AE diagnose. Lastly, one patient contacted us for withdrawal. Success rate was 99%. ICU: intensive care unit, EEG: electro-encephalogram, AE: acute encephalopathy.

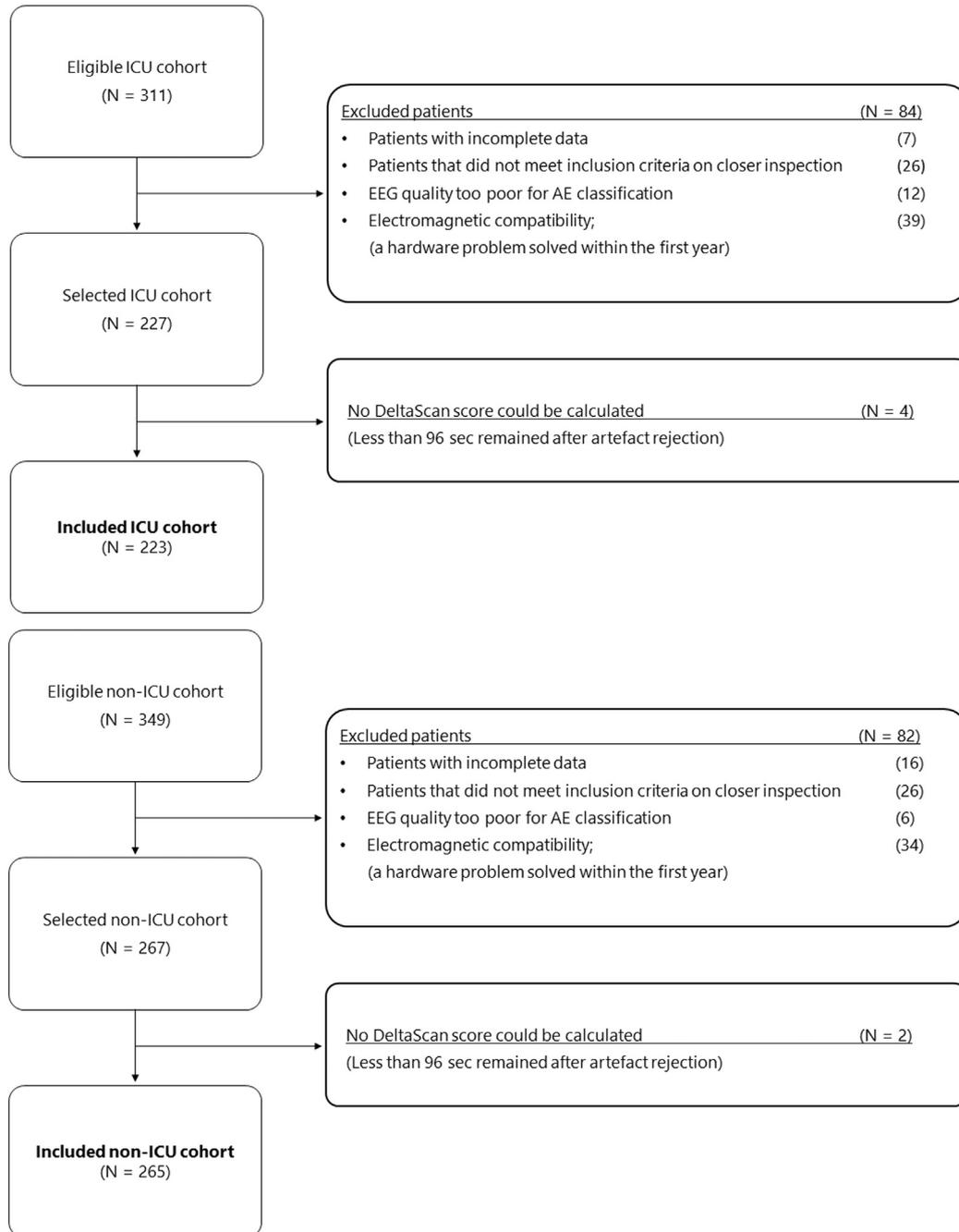
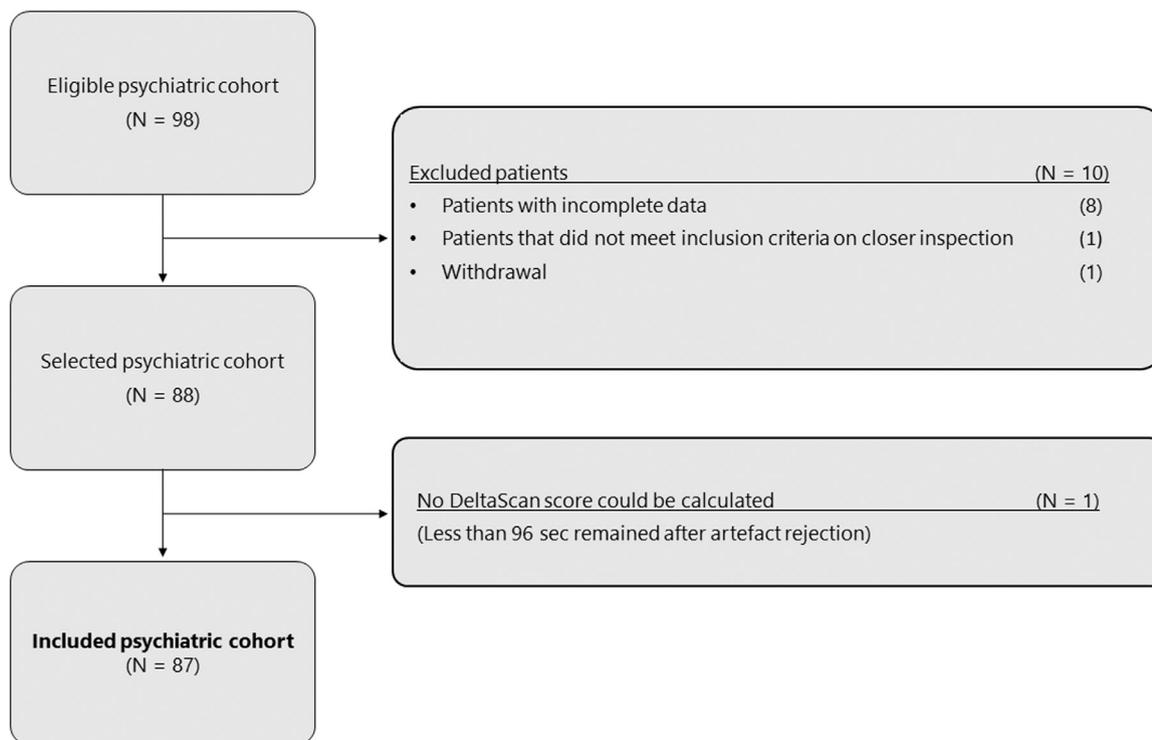


FIGURE 1. Continued



Performance in Acute Psychiatric Patients

We next determined the specificity of DeltaScan in a patient sample with an acute psychiatric disorder, without a diagnosis of delirium. Of the 98 eligible patients we included 88 (Fig. 1). For 87 patients, a DeltaScan score could be calculated (success rate 99%; participant flow is presented in Fig. 1). Within this sample, 50 patients (58%) were male, their mean age was 44 and 8 patients (9%) underwent electroconvulsive therapy (ECT). Twenty-five (29%) patients had psychotic spectrum disorders, 14 (16%) bipolar- and schizoaffective disorders, 16 depressive disorders (18%) and 32 (37%) patients were classified with another psychiatric diagnosis. None of these patients were diagnosed with delirium meaning only the specificity of the DeltaScan could be assessed. In this sample the DeltaScan had a specificity of 94% (95% CI = 87%–98%) with five false positives results (probability score of 3–4 [N = 2] and 2 [N = 3]).

CONCLUSIONS

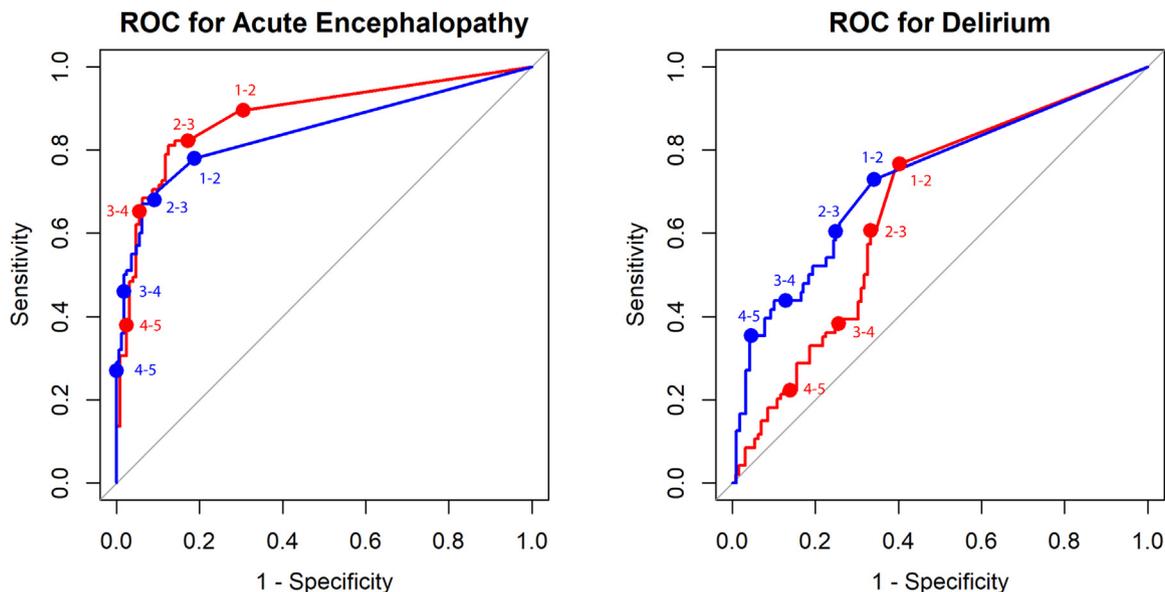
In this multicenter study we determined the performance of the DeltaScan, to detect AE and delirium. DeltaScan had a high success rate of 99%, (only six measurements rejected by built-in automated artifact rejection) and a good³⁴ repeatability (ICC = 0.82, 95% CI = 0.62–0.93). DeltaScan could detect AE and delirium with proper discrimination statistics in both ICU and non-ICU patients. It performed better in older patients, but performance was not affected by factors such as postoperative state, or psycho-active medication use, and we saw hardly any false positives in patients with a psychiatric disorders. Additionally, the occurrence of false positives was minimal in patients with psychiatric disorders, a population often challenging to distinguish clinically. This study contains one of the largest validation study populations (N = 494) for a delirium assessment tool and is the first one channel EEG device to provide real time output.

TABLE 1. Patient Characteristics

	Intensive Care			NonIntensive Care			Psychiatric Care
	Overall (N = 223)	Delirium (N = 94)	No Delirium (N = 129)	Overall (N = 265)	Delirium (N = 48)	No delirium (N = 217)	No delirium (N = 87)
Sex							
Male	150 (67%)	68 (72%)	82 (64%)	115 (43%)	20 (42%)	95 (44%)	50 (58%)
Female	73 (33%)	26 (28%)	47 (36%)	150 (57%)	28 (85%)	122 (56%)	36 (42%)
Age Median (IQR)*	68 (15)	69 (14)	67 (14)	79 (10)	81 (13)	79 (9)	44 (30)
Relevant medical history*							
Stroke	14 (6%)	6 (6%)	8 (6%)	21 (8%)	3 (6%)	18 (8%)	2 (2%)
Transient Ischemic Attack	12 (5%)	7 (7%)	5 (4%)	13 (5%)	3 (6%)	10 (4%)	4 (5%)
Alcohol abuses	9 (4%)	5 (5%)	4 (3%)	7 (3%)	0 (0%)	7 (3%)	3 (3%)
Traumatic intracranial bleeding	1 (0%)	1 (1%)	0 (0%)	4 (2%)	0 (0%)	4 (2%)	0 (0%)
Other intracranial disorders	9 (4%)	3 (3%)	6 (5%)	2 (1%)	0 (0%)	2 (1%)	5 (6%)
Medication 24 hours before measurement*							
Antipsychotics	56 (25%)	45 (48%)	11 (9%)	16 (6%)	13 (5%)	3 (1%)	39 (45%)
Alpha-2 antagonists	39 (17%)	27 (29%)	12 (9%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Benzodiazepines	43 (19%)	21 (22%)	22 (17%)	38 (14%)	7 (15%)	31 (14%)	46 (53%)
Opioids	66 (30%)	23 (24%)	43 (33%)	136 (51%)	24 (50%)	112 (52%)	0 (0%)
Medication 2 hours before measurement*							
Antipsychotics	10 (4%)	9 (10%)	1 (1%)	2 (1%)	2 (4%)	0 (0%)	0 (0%)
Alpha-2 antagonists	18 (8%)	14 (15%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Benzodiazepines	3 (1%)	1 (1%)	2 (2%)	4 (2%)	0 (0%)	4 (2%)	3 (3%)
Opioids	26 (12%)	9 (10%)	17 (13%)	17 (6%)	3 (6%)	14 (6%)	0 (0%)

Notes: Data are presented as number (n) and percentage (%) or median with interquartile range (IQR). Other neurological medical histories included: a removed intracranial cyst, sinus thrombosis, meningitis (5x), plagiocephalie, brain tumor (2x), multiple sclerosis, epilepsy (6x). Registered antipsychotics are haloperidol, olanzapine, quetiapine and clozapine. Registered alpha-2 antagonists are clonidine and dexmedetomidine. Registered benzodiazepines are: midazolam, lorazepam, temazepam, oxazepam, diazepam. Registered opioids are: morfine, fentanyl, remifentanyl, sufentanil, tramadol, piritramide, oxycodon. *Missing values: age 1 missing, relevant medical history 1 missing, medication 2 missings.

FIGURE 2. Performance of DeltaScan. Data are shown as value with 95% confidence interval (CI) for the Intensive Care Unit (ICU) — and the non-ICU —. AE: acute encephalopathy. AUROC: area under the receiver operating characteristic curve. NPV: negative predictive value. PPV: positive predictive value. The table presents the sensitivity, specificity, positive and negative predictive value based on positive (DeltaScan score 3–5) and negative results (DeltaScan score 1–2). The AUC for the ICU department did not significantly differ compared to the non-ICU department ($p = 0.262$ for AE and $p = 0.206$ for delirium).



There is growing interest in the use of minimal lead EEG-based delirium detection.¹³ Several studies^{35–37} showed similar performance of the DeltaScan, but required manual involvement of a researcher operating a computer to interpret the data, rather than providing automated output at the patient's bedside. Furthermore, a pretrained automated artifact detection algorithm was not applied in these other studies, which is critical for routine clinical application. Lastly, previous studies had a data-driven approach instead of validating a specific wave shape pattern associated with delirium¹⁸ that we trained and calibrated in two independent datasets.^{19,20,22}

Performance of AE detection in our calibration cohort study (AUC = 0.86, 95% CI = 0.81–0.90)²² was equal to the current study (AUC = 0.86, 95% CI = 0.83–0.90), but included only older, non-ICU patients and used a prototype of the device. These equivalent results imply robustness of the algorithm in diverse study populations. Validating DeltaScan as a delirium detector in the current study (AUC = 0.71, 95% CI = 0.66–0.75) produced comparable results to the calibration cohort as well (AUC of 0.78, 95% CI = 0.71

–0.85).²² A potential explanation for the slightly lower performance for delirium detection was that the delirium reference standard of the previous calibration study was based on standardized cognitive assessments stored on video, instead of classifying delirium based on descriptions of observations, the performance on the Delirium Interview and information from the EHR, as was done in the current study.

The phenomenon of patients with AE but without apparent delirium symptoms has drawn considerable interest.^{24,38,39} Perhaps there may be forms of AE that are not directly related to the delirium syndrome that EEG detects. Or it can be hypothesized that these cases might represent a prodromal phase of delirium or subsyndromal delirium, especially in challenging diagnostic situations such as with intubated patients. Supporting this hypothesis are their higher DRS-R-98 scores compared to those without AE or delirium.²¹ Additionally, AE has been independently associated with outcomes similarly impaired as those observed in delirium.^{15,35}

In contrast to robust DeltaScans performance to detect AE, delirium detection in younger patients was

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poorer (both regarding sensitivity as specificity) compared to older patients. Since our AE reference standard was based on the majority vote of three EEG experts visually inspecting the EEG, these results implicate that PDA and delirium symptoms have a weaker relation within this younger group. However, we should note that the study was not powered for this stratified analysis, and it should be highlighted that the estimated AUC difference between patients older and younger than 60 years should be interpreted with caution, given the wide confidence intervals of the estimates. An explanation could be that younger patients generally have a higher cognitive reserve⁴⁰ allowing them to have PDA without showing delirious symptoms leading to a higher false positive rate. Moreover, most clinical delirium tests used, have been validated in patients older than 60 years, and thus may perform poorer in younger patients.^{25,27,29,41,42}

A limitation of this study may be that the diagnosis of delirium, with which DeltaScan performance was compared, was not based on an examination by the expert him or herself. Instead, we used the majority vote of an expert panel that based its conclusion on description of observations of a trained researcher, the results of the previously validated Delirium Interview and information from the EHR.²⁵ We chose this approach (sensitivity 89%, specificity 82%),²⁵ as we previously observed large variation in the classification by individual delirium experts,¹¹ and diagnosis by a panel of experts examining patients together was difficult to organize, hampering inclusion of a large number of patients. A second limitation is that we excluded patients with known dementia, as chose the delirium diagnosis not to be blurred by possible dementia. It should be noted that dementia is relatively rare in Dutch hospitals as demented patients are not always referred for hospitalization.

Strengths of the study are that it included one of the largest validation study populations for a delirium assessment tool.^{7,43} Furthermore, our multicenter sample represents a heterogeneous population of both ICU and non-ICU patients from different clinical departments. Additionally, we evaluated DeltaScan's specificity in a population with acute psychiatric disorders other than delirium, where clinical differentiation of delirium can be challenging. Future research on AE and delirium detection should include patients with neurologic disorders such as dementia and

structural brain abnormalities. Furthermore, it would be interesting to study symptom fluctuation and its relation with EEG, since the severity of delirium may change over time. Lastly, monitoring long-term effects, including prognosis and mortality of patients with an abnormal level of PDA would provide important insights.

The DeltaScan is a fully automated device based on single-channel EEG that can accurately diagnose AE clinically manifesting as delirium within a few minutes at patient's bedside. This large and robust study suggests that DeltaScan could substantially aid in delirium detection within the hospital, as delirium is frequently missed, challenging to distinguish from other mental health conditions, and the existing questionnaire-driven detection tools are prone to inconsistencies between raters.

AUTHOR CONTRIBUTIONS

All authors confirmed their approval for the manuscript to be published. Study concept and design: FLD, SCAH, MB, MB, ES, AJCS. Acquisition of subjects and/or data: FLD, SCAH, MB, MB, FSSL, TN, MK, PJTR, CR, PFB, MC, RJO, MPP, ED, JWMK, KM, RF, AMV, AMK, BCM, AJ, E-JW, AMW, JP, SZ, HLK, ACDM, AB, WC, AJCS. Analysis and interpretation of data: FLD, SCAH, DMB, AJCS. Preparation of manuscript: FLD, S.CAH, MB, BCM, E-JW, ED, AJCS.

DATA STATEMENT

The abstract was presented in the form of a poster at the annual meeting of the European Delirium Association on 04-11-2022 where it won the best e-poster prize. Data can be obtained upon reasonable request.

DISCLOSURES

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The study design was conducted in accordance with the ethical principles that have their origin in the 2013 version of the Declaration of Helsinki⁴⁴ approved by the local

ethical committee of UMCU (17857) which waived the need for informed consent and registered at ClinicalTrials.gov (NCT03966274). This manuscript adheres to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.⁴⁵ During the preparation of this work the author(s) used AI in order to improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. Arjen JC Slooter is a non-salaried advisor for Prolira, a start-up company that develops the DeltaScan. Any (future) profits from EEG-based delirium detection will be used for future scientific research only. Frans SS Leijten is also a non-salaried advisor and holds shares in Prolira. The other authors report no conflicts with any product mentioned or concept discussed in this article.

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SUPPLEMENTARY MATERIALS

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References

- Gibb K, Seeley A, Quinn T, et al: The consistent burden in published estimates of delirium occurrence in medical inpatients over four decades: A systematic review and meta-analysis study. *Age Ageing* 2020; 49(3):352-360;doi:10.1093/ageing/afaa040
- Salluh JIF, Wang H, Schneider EB, et al: Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ (Online)* 2015; 350:1-10;doi:10.1136/bmj.h2538
- Ditzel FL, van Montfort SJT, Vernooij LM, et al: Functional brain network and trail making test changes following major surgery and postoperative delirium: a prospective, multicentre, observational cohort study. *Br J Anaesth* 2022; 1-8;doi:10.1016/j.bja.2022.07.054
- Kant IMJ, de Bresser J, van Montfort SJT, et al: Postoperative delirium is associated with grey matter brain volume loss. *Brain Commun* 2022; 5(1);doi:10.1093/braincomms/fcad013
- Tsui A, Searle SD, Bowden H, et al: The effect of baseline cognition and delirium on long-term cognitive impairment and mortality: a prospective population-based study. *Lancet Healthy Longev* 2022; 3(4):232-241;doi:10.1016/s2666-7568(22)00013-7
- Inouye SK, Westendorp RGJ, Saczynski Jane S: Delirium in elderly people. *Lancet* 2014; 383(9920):911-922;doi:10.1016/S0140-6736(13)60688-1.Delirium
- Neto AS, Nassar AP, Cardoso SO, et al: Delirium screening in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2012; 40(6):1946-1951;doi:10.1097/CCM.0b013e31824e16c9
- Boucher V, Lamontagne ME, Nadeau A, et al: Unrecognized incident delirium in older emergency department patients. *J Emerg Med* 2019; 57(4):535-542;doi:10.1016/j.jemermed.2019.05.024
- Van Eijk MM, Van Den Boogaard M, Van Marum RJ, et al: Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med* 2011; 184(3):340-344;doi:10.1164/rccm.201101-0065OC
- Van Eijk MMJ, Van Marum RJ, Klijn IAM, De Wit N, Kesecioglu J, Slooter AJC: Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med* 2009; 37(6):1881-1885; doi:10.1097/CCM.0b013e3181a00118
- Numan T, van den Boogaard M, Kamper AM, et al: Recognition of delirium in postoperative elderly patients: a multicenter study. *J Am Geriatr Soc* 2017; 65(9):1932-1938; doi:10.1111/jgs.14933
- Wilson JE, Andrews P, Ainsworth A, et al: Pseudodelirium: psychiatric conditions to consider on the differential for delirium. *J Neuropsychiatry Clin Neurosci* 2021; 33(4):356-364; doi:10.1176/appi.neuropsych.20120316
- Boord MS, Moezzi B, Davis D, et al: Clinical Neurophysiology Investigating how electroencephalogram measures associate with delirium : a systematic review. *Clin Neurophysiol* 2020; 132(1):246-257;doi:10.1016/j.clinph.2020.09.009
- Tanabe S, Mohanty R, Lindroth H, et al: Cohort study into the neural correlates of postoperative delirium: the role of connectivity and slow-wave activity. *Br J Anaesth* 2020; 125(1):55-66; doi:10.1016/j.bja.2020.02.027
- Kimchi EY, Neelagiri A, Whitt W, et al: Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. *Neurology* 2019;doi:10.1212/WNL.0000000000008164
- Jacobson SA, Leuchter AF, Walter DO, et al: Serial quantitative EEG among elderly subjects with delirium. *Biol Psychiatry* 1993; 34(3):135-140;doi:10.1016/0006-3223(93)90382-N
- Engel GL, Romano J: *Delirium, a syndrome of cerebral insufficiency (reprint)*. *JChronDis* 1959; 9:260-277
- Hughes CG, Pandharipande PP, Ely EW. *Delirium acute brain dysfunction in the critically ill.*; 2020.
- Van Der Kooij AW, Zaaij IJ, Klijn FA, et al: Delirium detection using EEG: what and how to measure. *Chest* 2015; 147(1):94-101;doi:10.1378/chest.13-3050

DeltaScan validation

20. Numan T, van den Boogaard M, Kamper AM, et al: Delirium detection using relative delta power based on 1-minute single-channel EEG: a multicentre study. *Br J Anaesth* 2019; 122(1):60-68;doi:10.1016/j.bja.2018.08.021
21. Hut SC, Dijkstra-Kersten SM, Numan T, et al: EEG and clinical assessment in delirium and acute encephalopathy. *Psychiatry Clin Neurosci* 2021; 0-3;doi:10.1111/pcn.13225
22. Ditzel FL, Hut SC, Dijkstra-Kersten SM, et al: An automated EEG algorithm to detect polymorphic delta activity in acute encephalopathy presenting as postoperative delirium. *Psychiatry Clin Neurosci* 2022; 76(12):676-678;doi:10.1111/pcn.13478
23. Slooter AJC, Otte WM, Devlin JW, et al: Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. *Intensive Care Med* 2020; 46:1020-1022;doi:10.1007/s00134-019-05907-4
24. Oldham MA: Delirium disorder: unity in diversity. *Gen Hosp Psychiatry* 2022; 74:32-38;doi:10.1016/j.genhosppsych.2021.11.007
25. Ditzel FL, Slooter AJC, van den Boogaard M, et al: The Delirium Interview as a new reference standard in studies on delirium assessment tools. *JAGS* 2023; 71:1923-1930;doi:10.1111/jgs.18263
26. American Psychiatric Association: DSM-5 diagnostic classification. Diagnostic and Statistical Manual of Mental Disorders, Washington D.C: American Psychiatric association, 2013 <https://doi.org/10.1176/appi.books.9780890425596.x00diagnosticclassification>
27. Bellelli G, Morandi A, Davis DHJ, et al: Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing* 2014; 43(4):496-502; doi:10.1093/ageing/afu021
28. Ely EW, Inouye SK, Bernard GR, et al: Delirium in mechanically ventilated patients. *JAMA* 2001; 286(21):2745-2746;doi:10.1001/jama.286.21.2745
29. Hart RP, Best AM, Sessler CN, et al: Abbreviated cognitive test for delirium. *Educ Res* 1997; 34(2):149-154;doi:10.1080/0013188920340206
30. Grover S, Agarwal M, Sharma A, et al: Symptoms and aetiology of delirium: a comparison of elderly and adult patients. *East Asian Arch Psychiatry* 2013; 23(2):56-64
31. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA: The delirium observation screening scale: a screening instrument for delirium. *Res Theory Nurs Pract* 2003; 17(1):31-50;doi:10.1891/rtnp.17.1.31.53169
32. Bergeron N, Dubois MJ, Dumont M, et al: Intensive care delirium screening checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001; 27(5):859-864;doi:10.1007/s001340100909
33. Buderer NM: Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. *Acad Emerg Med* 1996; 3(9):895-900; doi:10.1111/j.1553-2712.1996.tb03538.x
34. Koo TK, Li MY: A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016; 15(2):155-163;doi:10.1016/j.jcm.2016.02.012
35. van Sleuwen M, Sun H, Eckhardt C, et al: Physiological assessment of delirium severity. *Crit Care Med* 2021; 50(1):1-9; doi:10.1097/ccm.0000000000005224
36. Urdanibia-Centelles O, Nielsen RM, Rostrup E, et al: Automatic continuous EEG signal analysis for diagnosis of delirium in patients with sepsis. *Clin Neurophysiol* 2021; 132(9):2075-2082;doi:10.1016/j.clinph.2021.05.013
37. Yamanashi T, Crutchley KJ, Wahba NE, et al: Evaluation of point-of-care thumb-size bispectral electroencephalography device to quantify delirium severity and predict mortality. *Br J Psychiatry* 2022; 220(6):322-329;doi:10.1192/bjp.2021.101
38. Bowman EML, Cunningham EL, Page VJ, et al: Phenotypes and subphenotypes of delirium: a review of current categorisations and suggestions for progression. *Crit Care* 2021; 25(1):1-13; doi:10.1186/s13054-021-03752-w
39. Wilson JE, Mart M, Cunningham C, et al: Delirium. *Physiol Behav* 2020; 176(1):139-148;doi:10.1038/s41572-020-00223-4.Delirium
40. Balart-Sánchez SA, Bittencourt-Villalpando M, van der Naalt J, et al: Electroencephalography, magnetoencephalography, and cognitive reserve: a systematic review. *Arch Clin Neuropsychol* 2021; 36(7):1374-1391;doi:10.1093/arclin/aca132
41. Trzepacz PT, Mittal D, Torres R, et al: Validation of the delirium rating scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001; 13(2):229-242;doi:10.1176/jnp.13.2.229
42. Leentjens AFG, Schieveld JNM, Leonard M, et al: A comparison of the phenomenology of pediatric, adult, and geriatric delirium. *J Psychosom Res* 2008; 64(2):219-223;doi:10.1016/j.jpsychores.2007.11.003
43. Aldwikat RK, Manias E, Tomlinson E, et al: Delirium screening tools in the post-anaesthetic care unit: a systematic review and meta-analysis. *Aging Clin Exp Res* 2022; 34(6):1225-1235; doi:10.1007/s40520-021-02057-w
44. World Medical Association: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310(20):2191-2194;doi:10.1093/acprof:oso/9780199241323.003.0025
45. Cohen JF, Korevaar DA, Altman DG, et al: STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; 6(11):1-17;doi:10.1136/bmjopen-2016-012799