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Applicability of NeuroTrend as a bedside monitor in the neuro ICU

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HIGHLIGHTS

- Proposal and guidance on how a computer algorithm may be used by ICU staff as a cEEG bedside monitor.
- High interrater agreement among nurses for EEG patterns that may indicate subclinical seizures.
- Large amount of prospectively recorded, randomized long-term video EEG data from two neuro ICUs.

ABSTRACT

Objective: To assess whether ICU caregivers can correctly read and interpret continuous EEG (cEEG) data displayed with the computer algorithm NeuroTrend (NT) with the main attention on seizure detection and determination of sedation depth.
Methods: 120 screenshots of NT (480 h of cEEG) were rated by 18 briefly trained nurses and biomedical analysts. Multirater agreements (MRA) as well as interrater agreements (IRA) compared to an expert opinion (EXO) were calculated for items such as pattern type, pattern location, interruption of recording, seizure suspicion, consistency of frequency, seizure tendency and level of sedation.
Results: MRA as well as IRA were almost perfect (80–100%) for interruption of recording, spike-and-waves, rhythmic delta activity and burst suppression. A substantial agreement (60–80%) was found for electrographic seizure patterns, periodic discharges and seizure suspicion. Except for pattern localization (70.83–92.26%), items requiring a precondition and especially those who needed interpretation like consistency of frequency (47.47–79.15%) or level of sedation (41.10%) showed lower agreements.
Conclusions: The present study demonstrates that NT might be a useful bedside monitor in cases of subclinical seizures. Determination of correct sedation depth by ICU caregivers requires a more detailed training.
Significance: Computer algorithms may reduce the workload of cEEG analysis in ICU patients.

Abbreviations: AC1, Gwet's multirater agreement coefficient of first-order; AIT, Austrian Institute of Technology; aEEG, amplitude integrated electroencephalography; BMA, biomedical analyst; BS, burst suppression; CCET, American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology; cEEG, continuous electroencephalography; ESP, electrographic seizure pattern; EXO, expert opinion; FIRDA, frontal intermittent rhythmic delta activity; GCS, Glasgow coma scale; ICU, intensive care unit; IRA, interrater agreement; MRA, multirater agreement; NT, NeuroTrend; PD, periodic discharge; qEEG, quantitative electroencephalography; RAA, rhythmic activity in the alpha range, "rhythmic alpha activity"; RDA, rhythmic delta activity; RDA+S, rhythmic delta activity plus seizures; RTA, rhythmic activity in the alpha range, "rhythmic theta activity"; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges; SW, spike wave.

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1. Introduction

Continuous electroencephalography (cEEG) is used in the intensive care unit (ICU) to detect subclinical seizures and to monitor sedation depth in cases of refractory seizures or elevated intracranial pressure (Eisenberg et al., 1988; Friedman et al., 2009; Sutter et al., 2013). Previous studies showed that subclinical seizures occur more often than anticipated in the ICU (Kaplan, 1999) and frequently develop at an early stage of acute brain injury (Claassen et al., 2004). Since mortality increases exponentially with seizure duration in critical care patients, proper application and instant interpretation of cEEG is crucial in this setting (Young

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et al., 1996; Vespa et al., 1999). Its use has been associated with a favorable outcome in the critically ill (Ney et al., 2013). But cEEG monitoring is not available in the majority of hospitals as it requires a lot of resources.

To minimize the diagnostic effort of visually screening hours of cEEG the Austrian Institute of Technology (AIT) has developed a computer algorithm called NeuroTrend (NT) with a strong ability to visualize rhythmic and periodic patterns in a time compressed fashion (Fürbass et al., 2015, 2016). A possible field of application lies in the use of NT as a bedside monitor. However, in contrast to other ICU monitors, an automatic alarm system for seizures would be ineffective, as false alarms would be too frequent in an environment that contains a plurality of possible EEG artefacts. In addition, NT data needs interpretation as it also displays trend data of patterns that are not clearly ictal. Therefore, trained nurses, taking care of the same patient over several hours would be best suited to use and interpret the computer results.

The present study investigated whether briefly trained ICU caregivers can read and interpret NT cEEG data correctly. To test this hypothesis, 15 ICU nurses and 3 biomedical analysts (BMA) not familiar with EEG, had to evaluate NT cEEG data from patients with acute brain injury. The evaluations were then compared between the respondents as well as with an expert opinion (EXO) and tested for their consistency. The main parameters tested for consistency were: (1) Identification of seizures occurrence and seizure progression (2) Assessment of the sedation depth.

2. Methods

2.1. Dataset

A dataset of 83 prospectively recorded continuous video-EEGs (6733 h, mean 73 h) from a neurological (Neurological Center Rosenhuegel) and a neurosurgical ICU (General Hospital Vienna) was used. All recordings were obtained from patients older than 18 years with a median age of 58.5 years. EEGs were recorded using a Micromed EEG system (SystemPLUS Evolution 1.04.95, Micromed S.p.A., Veneto, Italy) with a sampling rate of 256 Hz, placing 21 electrodes according to the international 10–20 system. Only video-EEGs with a duration of more than 24 h and a sufficient EEG signal quality over the whole recording period were used in this study. Patients were selected using the NeuroTrend (NT) Analysis Database. This database was established in 2011 with its main focus of investigating rhythmic and periodic EEG patterns of 'ictal-interictal uncertainty' as well as subclinical seizures and status epilepticus (Koren et al., 2015). All cEEGs registered in the database were reviewed by board certified neurophysiologists and screened for electrographic seizure patterns (ESP), spike wave (SW), rhythmic delta activity (RDA), periodic discharges (PD), burst suppression (BS) patterns and patterns mimicking artefacts as described elsewhere (Herta et al., 2015). EEG changes in frequency, prevalence, localization and morphology were reevaluated every 24 h according to the guidelines of the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (CCET) (Hirsch et al., 2013). Additional information included treatment protocols, patient characteristics, certain neurologic scores and follow up data (Glasgow Outcome Score after six month). From this database 20 patients were randomly selected with a predefined split into the following six groups: PD ($n = 3$), ESP ($n = 3$), SW ($n = 3$), RDA ($n = 3$), BS ($n = 3$) and none of the above-mentioned patterns ($n = 5$). If a patient showed more than one pattern type he or she could be randomized into multiple groups but overall could not be selected more than once.

2.2. NeuroTrend

Included cEEGs were analyzed by the computer algorithm NT. This algorithm detects and visualizes rhythmic and periodic EEG patterns with a strong emphasis on data and time compression as well as artefact rejection (Hartmann et al., 2014; Fürbass et al., 2015, 2016). A color code displays the following patterns: periodic discharges (PD), rhythmic delta activity (RDA), rhythmic delta activity plus superimposed sharp waves or spikes (RDA + S), rhythmic activity in the theta range (RTA), rhythmic activity in the alpha range (RAA) and spike wave (SW). Pattern localization, pattern frequencies, frequency bands (beta, alpha, theta and delta range) and amplitude integrated EEG (aEEG) are calculated and displayed on a graphical user interface. The definition of rhythmic and periodic EEG patterns follows the guidelines of the CCET adding unequivocal electrographic seizures including generalized spike-wave discharges at 3 Hz or faster, evolving discharges that reach frequencies of more than 4 Hz as well as BS patterns (Hirsch et al., 2013). A validation of NT was recently published elsewhere (Herta et al., 2015). NT is part of the encevis software package. Version V1.3 of encevis was used in this study (http://www.encevis.com).

2.3. NT training and data preparation

Nurses and BMAs (in the following referred to as "respondents") from a neurosurgical ICU were asked to volunteer for the study. A total of 18 respondents, including 3 BMAs and 15 nurses, then compiled a questionnaire where they were asked about work experience, experience with EEG, computer skills, experience in playing computer games and presence or absence of color blindness. All personal data were anonymized for further analysis. All respondents underwent a brief educational course of approximately one hour. Features of NTs graphical user interface and the study design were explained. Samples of cEEG and NT data were presented. The presentation files as well as a short rating manual were handed out to the respondents (available as Supplementary material).

Shortly thereafter each respondent was asked to rate the preselected NT data. The rating manual could be used during the evaluation process. During the assessment, the time needed to evaluate the NT data of 20 patients was measured. NT data were presented to the respondents by an editable Microsoft® PowerPoint slideshow (Fig. 1). A brief patient history was given, including information about admission diagnosis, operative procedures undertaken and their time course, seizures prior to EEG, anesthetics and antiepileptic drugs administered, clinical features that may indicate subclinical seizures (Husain et al., 2003) and Glasgow Coma Scale (GCS) at cEEG start. Subsequently, results of NT analysis were presented in a mask that allowed simultaneous ratings of each slide. Slides displayed 6 consecutive NT screenshots for each patient with a length of 4-h each, giving in total 120 screenshots or 480 h of cEEG.

2.4. NeuroTrend review scheme

Rating possibilities were grouped into 4 categories and could be selected by check boxes. In category one the patterns recognized by NT (PD, RDA, RDA + S, RTA, RAA, SW) had to be identified (Fig. 1a). The selection of multiple patterns for each 4-h segment was possible. For each pattern the principal location had to be defined. If the pattern was not clearly localized to the left or right hemisphere, generalized had to be selected. Furthermore, for each pattern the consistency of frequency had to be indicated (Fig. 1b). A consistent frequency was assumed if the frequency remained the same or increased/decreased continuously over a longer recording period of at least 30 min.

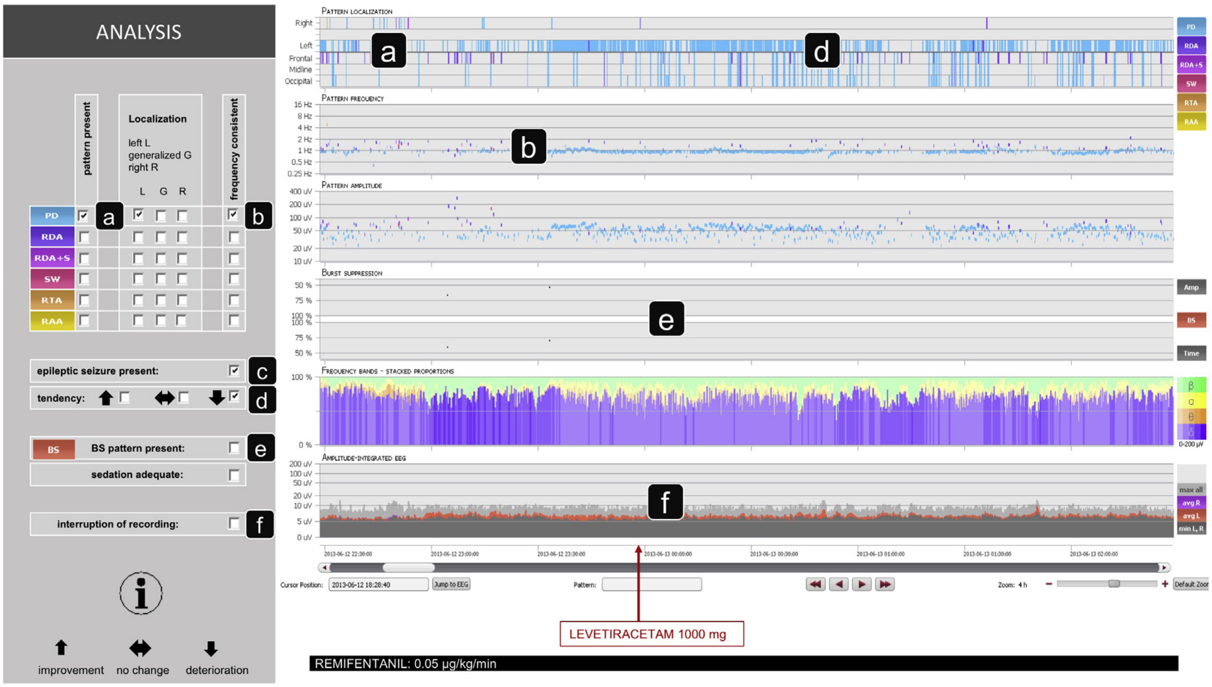

Fig. 1. Example of a rating slide. The slide is divided into two parts. On the right side a 4-h sample of NeuroTrend (NT) with additional information concerning anesthetics and antiepileptic drugs is presented to the respondent. On the left side a rating matrix which is divided into four categories was implemented (white boxes). The information sign at the left bottom gives the respondent a short summary about the medical record of the patient. In this case a comatose patient suffered from subclinical seizures due to a large left parietal metastasis of a lung carcinoma. EEG was used during the weaning process after resection of the metastasis. Even after resection the NT screenshot displays left sided periodic discharges (PD) (a) with a stable frequency (b) which was interpreted as ongoing seizure activity (c). Because of an increase in pattern occurrence (PD) the tendency was rated as "seizure deterioration" (d). No burst suppression (BS) occurred during the recording period (e). EEG was continuously recorded as there is no discontinuity in the aEEG (f).

In the second category respondents had to check if they suspected a seizure (Fig. 1c). Seizures were defined by presence of SW, RTA and/or RAA. More equivocal patterns like PD, RDA and RDA + S had to be rated as possible seizures if these patterns occurred continuously over a long-time period with a consistent frequency. This definition was established in order not to oversee the third non-convulsive seizure criterion introduced by Chong et al. which includes sequential rhythmic, periodic, or quasi-periodic waves at 1/sec with an unequivocal evolution in frequency, morphology or location (Chong and Hirsch, 2005). If seizures were present the tendency (unchanged, improvement, deterioration) between the current and the consecutive slide of a patient had to be specified (Fig. 1d). Improvement was defined by absence of seizures or a decline in seizure frequency. Deterioration was defined by occurrence of new seizures or increase of seizure frequency.

BS patterns could be selected in category three (Fig. 1e). In case of BS it had to be specified if anesthesia depth was adequate. Anesthesia depth was defined as adequate if: (1) the BS pattern occurred with a nearly simultaneous change in the anesthetic regimen after seizures were treated. (2) If the BS pattern were present while the patient suffered from elevated ICP. Administered anesthetics were displayed under the timeline of the NeuroTrend interface. Elevated ICP was mentioned in the patient history.

Finally, in category four, respondents had to choose if an interruption of the recording had occurred, best seen in an abrupt discontinuation of the aEEG (Fig. 1f).

The same editable slideshow was evaluated by a board-certified neurophysiologist who was familiar with NT. Not only NT results but also the raw EEG and chart reviews were accessible to the neurophysiologist during the rating process to establish an "expert opinion" (EXO).

For further analysis, the NT detections of type RDA and RDA + S were merged into RDA and RTA and RAA into ESP. There was no reason to differentiate these patterns for the present study.

2.5. Statistical evaluation

For statistical evaluation, an interrater agreement (IRA) was calculated. Seven independent, as well as twenty dependent items, were assessed by the IRA. Independent items included occurrence of specific patterns (SW, PD, RDA, ESP, BS), seizure suspicion and interruption of recording. Dependent items included seizure tendency, pattern localization and adequacy of BS. The terms "dependent items" and "independent items" refer to the fact that dependent items serve to further describe and sub-classify independent items. For example, if we choose a specific pattern like "SW" as the independent item, it can be further sub-classified by the dependent item "pattern localization" into "lateralized" or "generalized".

To categorize the IRA, ranges of agreement have been defined as 0.01–0.20 for a slight agreement, 0.20–0.40 for a fair agreement, 0.40–0.60 for a moderate agreement, 0.60–0.80 for a substantial agreement and 0.80–1.00 for a perfect agreement (Blood and Spratt, 2007). To quantify the rating agreement of the respondents Gwet's multirater agreement coefficient of first-order (MRA AC1) was used (Gwet, 2014). The same method was used to measure the rating agreement in each category between the respondents with the EXO (IRA AC1). All IRA AC1 were then averaged over the respondents to allow further comparisons that consider the whole study population. The same approach was used for dependent items if the precondition (independent item) of the respondent met the precondition of the EXO. Because of a given EXO, sensitivity and specificity of all rating items were calculated for every respondent. The respondents' answer was counted as a true positive or a true negative if there was an agreement with the EXO. Furthermore, for each respondent individual performance scores were calculated. The individual performance score was composed by the averaged IRA between a respondent and the EXO of all independent items excluding the item "disruption of recording". Only independent items were used for this analysis because the number of ratings was equal for all respondents. The individual performance score was used to determine differences and correlations in the rating behavior of the respondents. Sex, profession, preexisting experience with EEG and computer gaming experience were evaluated by an independent two-sided t-test. Computer skills were assessed by a one-way analysis of variance. Pearson correlation coefficient was used for age and work experience (in years). Significance levels of 0.05 were applied for all statistical tests.

The two non-binary items "seizure tendency" and "pattern localization" were displayed using confusion matrices. For each item the percentage of agreement (true positive and true negative ratings to all ratings) for every available category was presented as a heat map and compared with the EXO ratings.

Statistical calculations were performed by using MATLAB (The MathWorks, Natick, MA, U.S.A.) and its Statistics toolbox as well as IBM SPSS Statistics V23.

2.6. Ethics approval and consent

The study protocol was approved by the institutional ethics commission. Informed consent was given by all nurses and BMAs that volunteered for the study. Patients included in the NT database were mainly not able to give consent during EEG recordings. Therefore, the ethics commission requested that all patients that were not able to give consent and their relatives receive a written patient information and/or were informed about the study and the possibility to withdraw their personal data in the future.

3. Results

The mean time for the evaluation of the 120 screenshots was 1 h and 22 min. In Table 1 the IRA of dependent as well as independent items is shown. We observed the following multirater agreement coefficients (MRA AC1) for independent items: interruption of recording (92.72%), spike wave (91.74%, SW), rhythmic delta activity (85.53%, RDA) and burst suppression (80.39%, BS) showed perfect agreements, while electrographic seizure patterns (69.91%, ESP), periodic discharge (66.82%, PD) and seizure suspicion (60.9%) showed substantial agreements. All independent items also were compared to the "expert opinion" (EXO) by averaging the interrater agreement (IRA) of the respondents. As expected, slightly higher IRAs could be achieved with a perfect agreement for interruption of recording (93.97%), SW (92.03%), RDA (90.25%) and BS (85.63%). Again, a substantial agreement was observed for ESP (77.96%), PD (74.93) and seizure suspicion (67.45%). Fig. 2 illustrates the differences between the multirater agreement (MRA) and the averaged IRA of the respondents compared to the EXO. We observed that independent items with a high MRA like SW or interruption of recordings do not differ as much from the EXO as items with a lower MRA like seizure suspicion. Similar effects were obtained in the receiver operating characteristic of all independent items (Fig. 3A). Seizure suspicion (79.10%), ESP (88.69%) and PD (87.98%) achieved lower specificities under 90% in comparison with SW (95.33%), BS (92.44%); RDA (93.88%) and interruption of seizures (99.04). Except PD (79.25%) all items obtain sensitivities over 80% with RDA (93.18%) and BS (92.82%) exceeding sensitivities of 90%.

In general, dependent items showed lower agreements as independent items with a perfect agreement for the localization of ESP (92.26%) and substantial agreements for the localization of PD (75.68%), the localization of SW (71.81%), the localization of RDA (70.83%) and seizure tendency (61.40%) (Table 1). Assessment of frequency consistency was highly dependent on the evaluated pattern type and showed agreements between 47.47% and 79.15%. The question whether the level of sedation was adequate in the presence of BS patterns achieved only a barely moderate agreement (41.10%). Dependent items with more than two choices are displayed as confusion matrices in Fig. 4. We obtained an acceptable result with a diagonal line of agreement for seizure tendency (Fig. 4B). All patterns were analyzed for pattern localization (Fig. 4A). We observed that generalized patterns were distinguished clearly from lateralized patterns but in many cases respondents could not assign the correct side for lateralized patterns.

Fig. 5 gives a detailed overview of all assessed items. Agreements of every single respondent compared to the EXO are displayed as a heat map. For every respondent, the individual performance score is displayed next to the respondent rank. Accordingly, Fig. 3B depicts how sensitive and specific the respondents' ratings were.

The respondent characteristics including sex, age, profession, gaming experience, EEG experience, work experience or computer

Table 1
Interrater and multirater agreement for tested items.

Item	Dependent item	Choices	Multirater agreement, AC1 (%)	Averaged IRA to EXO, AC1 (%)
Periodic discharge		Yes, no	66.82	74.93
	Localization	L,G,R		75.68
	Consistency of frequency	Yes, no		47.47
Rhythmic delta activity		Yes, no	85.53	90.25
	Localization	L,G,R		70.38
	Consistency of frequency	Yes, no		79.15
Spike wave		Yes, no	91.74	92.03
	Localization	L,G,R		71.81
	Consistency of frequency	Yes, no		64.53
Electrographic seizure pattern		Yes, no	69.91	77.96
	Localization	L,G,R		92.26
	Consistency of frequency	Yes, no		79.63
Burst suppression		Yes, no	80.39	85.63
	Level of sedation	Adequate, inadequate		41.10
Seizures suspicion		Yes, no	60.90	67.45
	Seizure tendency	T+, T=, T−		61.40
Interruption of recording		Yes, no	92.72	93.97

AC1, agreement coefficient of first order; EXO, expert opinion; IRA, interrater agreement; L, left; R, right; G, generalized; NA, not available; T+, improvement; T=, unchanged; T−, deterioration.

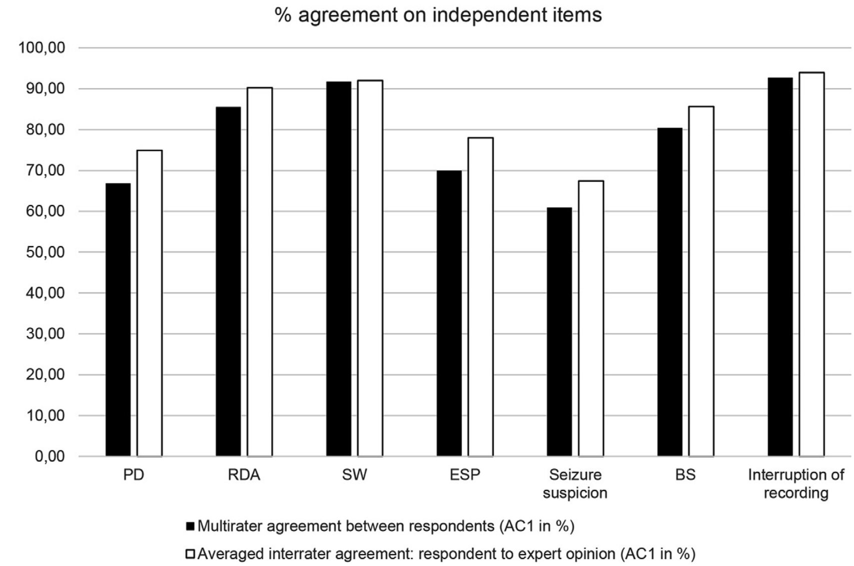

Fig. 2. Percentage of agreement (% agreement) on independent items. The multirater agreement coefficient of first order (MRA AC1; black bars) gives the agreement between the respondents. The interrater agreement coefficient of first order (IRA AC1; white bars) presents the averaged agreement between the respondents and the expert opinion. BS, burst suppression; PD, periodic discharge; RDA, rhythmic delta activity; ESP, electrographic seizure pattern; SW, spike wave.

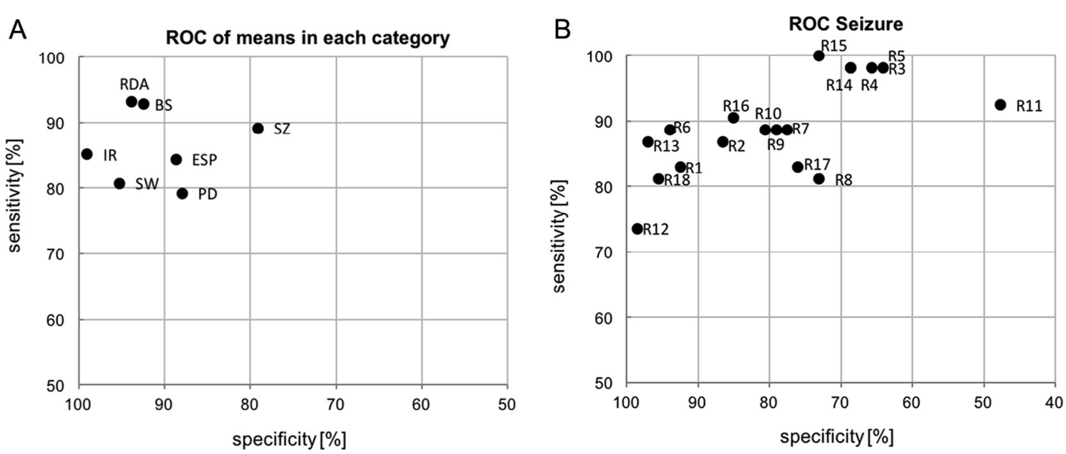

Fig. 3. Receiver operating characteristic. (A) shows the mean sensitivity and mean specificity for seven independent items calculated from the answers of 18 respondents. (B) illustrates the sensitivity and specificity for seizures of every respondent (R). To calculate sensitivity and specificity answers of the respondents were compared to the expert opinion. BS, burst suppression; PD, periodic discharge; RDA, rhythmic delta activity; ESP, electrographic seizure pattern; SW, spike wave; IR, interruption of recording; SZ, seizure suspicion; R, respondent.

skills had no significant influence on the individual performance score of each respondent. A detailed overview of characteristics, statistical tests used and results is given in Table 2. No respondent suffered from color blindness.

4. Discussion

The applicability of NeuroTrend (NT) as a continuous EEG (cEEG) bedside monitor was evaluated by multirater agreement (MRA) and interrater agreement (IRA). Perfect agreement was found for spike waves (SW), rhythmic delta activity (RDA) and burst suppression (BS) while electrographic seizure patterns (ESP), periodic discharges (PD) and seizure suspicion achieved substantial agreement among the respondents. Similar agreements were found when we compared the choices of the respondents with the expert opinion (EXO). Furthermore, sensitivity and specificity for all independent items showed results over 80% with two exceptions: sensitivity for PD with 79.25% and the specificity for seizure suspicion with 79.10%. These high agreements, high sensitivities and high specificities achieved for independent items indicate that with NT, briefly trained ICU personal can identify the occurrence of rhythmic and periodic EEG patterns that may indicate seizures. Also, over or under dosage of sedative drugs may be identified adequately.

NT displays trend data and not every short-lasting detection should be interpreted as an event. This provides an opportunity for interpretation and raises the question why some patterns showed higher agreements than others. SW and RDA had the highest agreements because they were mostly present over longer time periods and were therefore easy to detect, if displayed by the algorithm. The same is true for BS patterns where in some cases interpretation was facilitated if large amounts of anesthetic drugs were administered at the same time the pattern occurred. One possible source of error could have been that anesthetic drugs given at short notice for nursing care caused short periods of BS. Respondents knew only about the continuous application of intravenous anesthetics and were blinded to these short applications. This might have caused disagreement during the rating process. PD were the most difficult to evaluate pattern. PD occurred frequently with lots

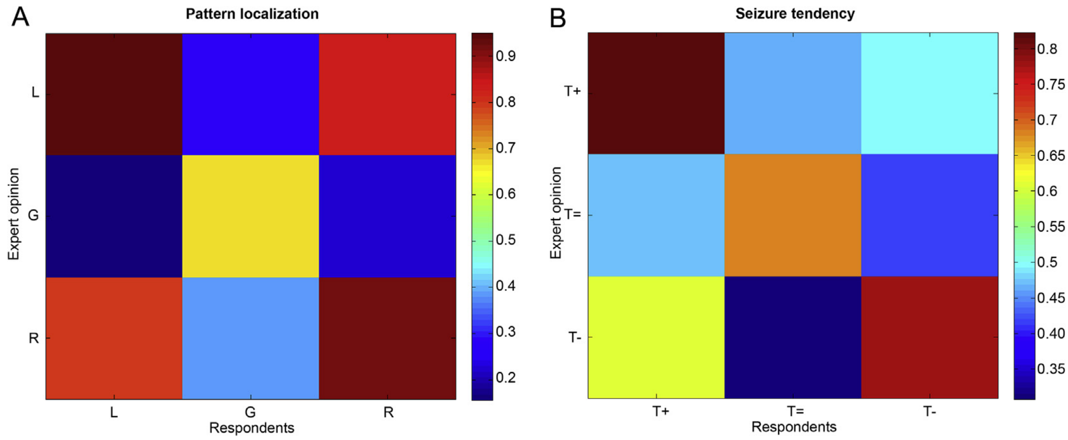

Fig. 4. Color coded confusion matrices for dependent items with more than two choices. Choices are shown on the vertical and horizontal axes while heat map intensities indicate the percentage of respondents choosing an available option. Only annotations were used if the required dependent item was previously chosen correctly. A dark red diagonal line from upper left to lower right would indicate a perfect result. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

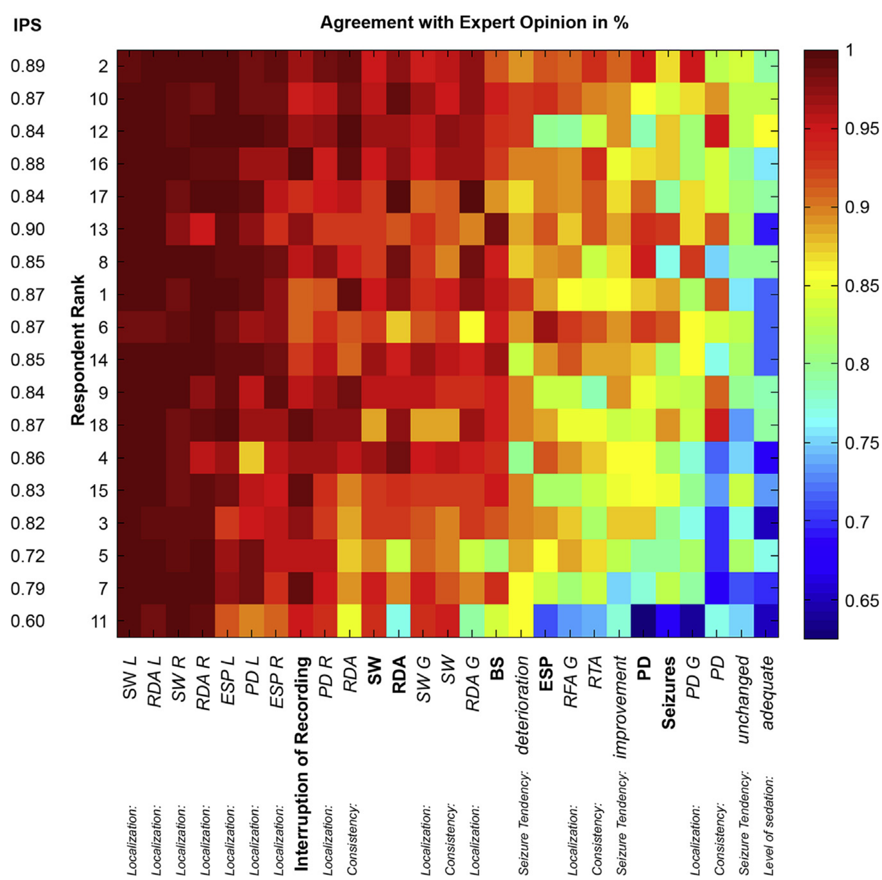

Fig. 5. The heatmap shows detailed individual scores of agreement coded by color according to the color bar on the right. For each respondent seven independent items (bold) and twenty dependent items (italic) have been tested. Scores for each item are calculated as percentage of answers in agreement between the respondents and the expert opinion. Additionally, on the left the individual performance score (IPS) of each respondent is displayed which takes all independent items except interruption of seizures into account. BS, burst suppression; PD, periodic discharge; RDA, rhythmic delta activity; ESP, electrographic seizure pattern; SW, spike wave; G, generalized; L, lateralized to the left; R, lateralized to the right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of short-lasting detections. Only PD with a consistency in frequency over a period of 30 min should selected. This created a great scope for interpretation for example f single patterns appeared successively over longer periods of time. ESP on the contrary are patterns that are very rarely displayed incorrectly by NT. The difficulty is that these patterns, if present, mostly occurred in short periods of time and were therefore difficult to distinguish from misdetections resulting in an agreement of 77.96%.

Obviously, items that needed interpretation like seizure suspicion, seizure tendency, consistency of frequency and level of sedation showed lower MRAs/IRAs than items that had to be selected by mere presence, no matter if items were dependent or indepen-

Table 2
Influences of respondent characteristics on the individual performance score.

Respondent characteristics (n = 18)	Number of /mean	Statistical test	P value (α = 0.05)
Sex	Male: 5 Female: 13	Independent t-test of unequal variance	ns (0.141)
Age (in years)	$\bar{x}$ = 35.44	Pearson's correlation coefficient (0.033)	ns (0.909)
Profession	Nurse:15 BMA: 3	Independent t-test of unequal variance	ns (0.514)
Gaming experience	Available: 10 Not available: 8	Independent t-test of unequal variance	ns (0.828)
EEG experience	Available: 3 Not available: 15	Independent t-test of unequal variance	ns (0.514)
Work experience (in years)	$\bar{x}$ = 8.83	Pearson's correlation coefficient (−0.006)	ns (0.958)
Computer skills	Very good: 2 Good: 10 Satisfactory: 6 Sufficient: 0 Not sufficient: 0	One way ANOVA	ns (0.623)

ANOVA, analysis of variance; BMA, biomedical analyst; ns, not significant.

dent. Here we want to emphasize that only a brief presentation of the study protocol was chosen to train the respondents. This approach was not only chosen to recruit as many respondents as possible but also in order to test the feasibility and usability of our newly designed NT review scheme for nurses. We are convinced that better agreements are achievable with longer and repetitive trainings, especially for items that demand interpretation. Moreover, it has to be emphasized that the less well recognized dependent item "consistency of frequency" might have had a negative influence on the ratings of seizure suspicion and seizure tendency for patterns like PDs and RDA as they needed a consistent frequency to classify for seizures.

The strengths of our study are (1) the large amount of prospectively collected continuous EEG data, (2) a large number of respondents who rated the NT results and (3) a study design that is implementable in everyday clinical life. Implementation is not only possible from a technical point of view but also because we presented an applicable NT review scheme for ICU staff members. On the one hand, most of the nurses and biomedical analysts (BMA) at our hospital work in 12-h shifts, making it easy and feasible to check the NT monitor every 4 h. On the other hand, a 4-h period is easily readable on the NT screen and small EEG changes are still detectable. The mean time it took the respondents to evaluate the 120 slides was 1 h and 22 min. Therefore, a brief screening of a 4-h segment is not time consuming and can be completed in less than one minute.

The short time period in which respondents had to learn and understand the assessment process may be an advantage in terms of simulating 'real life' conditions but also limits our conclusions concerning items that needed more interpretation and instructions. For example, the independent item BS showed a perfect MRA and IRAs. In contrast the corresponding and therefore dependent item 'level of sedation' had an IRA of only 41.10%. In our study protocol an adequate level of sedation was defined by the occurrence of BS patterns at the time a patient suffered from ongoing seizures or showed an elevated ICP. The low level of agreement in this case reflects the insecurities concerning certain definitions that had not been sufficiently internalized by the respondents.

Automatic seizure detection is still rarely used in the ICU because of the many false alarms. NeuroTrend therefore tries to present the complex EEG in simplified form. When it comes to abnormalities, trained staff will alert the specialist. Ideally, a learning process should be initiated and the rate of false alarms should be reduced. This has yet to be verified in future studies. Our experience has shown that increased awareness increases the number of detected seizures in the ICU. Whether this results in over treatment is still to be evaluated and currently discussed by experts (Jordan and Hirsch, 2006; Ferguson et al., 2013).

Artefacts were neglected in the study because they were (1) either detected by the algorithm and removed, or (2) of such a short duration that they did not meet the seizure criteria of the study. Likewise, patterns such as frontal intermittent rhythmic delta activity (FIRDA) and stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs), which are frequently encountered in the ICU, have not been dealt with in detail, since it is always necessary to carry out a careful medical examination in case of seizure suspicion. Thus, an initial alert by the nursing staff, even if it is a false alarm, is welcome if these patterns occur.

Because we wanted to simplify the rating process, next to the pattern types SW, RDA, PD and BS we implemented the term ESP where we summarized fast, rhythmic and unequivocal seizure patterns in the alpha and theta range (labeled "rhythmic theta activity; RTA" and "rhythmic alpha activity; RAA" in NT) according to CCET and non-convulsive seizure criteria (Chong and Hirsch, 2005; Hirsch et al., 2013). These patterns are highly suspicious for the presence of subclinical or non-convulsive status epilepticus in neurological critical care patients, because normal alpha activities nearly never occur in this highly selective patient cohort. Furthermore, pathological alpha and theta patterns like alpha and theta coma would be misinterpreted by the algorithm but at least recognized by the responsible physician (Westmoreland et al., 1975; Synek and Synek, 1984). Therefore, and to simplify matters for the respondents involved we defined the NT labels "rhythmic theta activity" (RTA) and "rhythmic alpha activity" (RAA) as clear seizure patterns aware of a possible error. Another weakness of the study is that only one neurophysiologist formed the EXO. However, this shortcoming must be put into relation, since the study is about the recognition and interpretation of displayed patterns and not about the assessment of the computer algorithm itself.

Overall, we believe patients may benefit from the use of computer algorithms like NT as a bedside monitor. We showed that most ICU staff members can easily read and interpret the NT results after a brief training with no restrictions concerning their age, their computer skills or their work experience. Ultimately, this may lead to an increased use of continuous EEG at ICUs as well as to an increased awareness of frequently occurring subclinical seizures and non-convulsive status epilepticus. In many ICUs cEEG is not applied because of the enormous amount of data and the resulting effort of tedious interpretation. NT can facilitate and fasten the evaluation process and with the help of trained ICU personnel cEEG may lose its arduous character and develop into an easy applicable, non-invasive tool to detect seizures and monitor sedation depth.

5. Conclusion

In the present study, the applicability of a computer algorithm called NeuroTrend (NT) as a bedside monitor for ICU patients who undergo long-term EEG monitoring was assessed. In this specific scenario, NT results were assessed by briefly trained nurses ($n = 15$) and biomedical analysts ($n = 3$). Occurrence of patterns that could indicate seizures as well as evaluation of sedation depth were of particular interest. Detection of seizure patterns showed perfect to substantial agreement in the multirater (MRA) as well as the interrater agreement (IRA). While burst suppression (BS) patterns were clearly identified among the respondents the interpretation of an adequate sedation could only reach moderate agreement. We therefore assume that NT is perfectly suited as a bedside neuro-monitor used by various ICU staff members if an adequate amount of time is invested in staff trainings.

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Algorithm development was conducted by the "Austrian Institute of Technology" including the authors Franz Fürbass and Manfred Hartmann. The Austrian Institute of Technology is the manufacturer of the EEG software package "encevis", which will include the NeuroTrend algorithms.

Christoph Baumgartner, Andreas Gruber, Angelika Zöchmeister and Arthur Hosmann declare that they have no conflict of interest related to the present work.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2017.04.002.

References

Blood E, Spratt KF. Disagreement on agreement: Two alternative agreement coefficients. Paper 186–2007. SAS Global Forum 2007:1–12.
Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J. Clin. Neurophysiol. 2005;22:79–91.
Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62:1743–8.
Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J. Neurosurg. 1988;69:15–23.
Ferguson M, Bianchi MT, Sutter R, Rosenthal ES, Cash SS, Kaplan PW, et al. Calculating the risk benefit equation for aggressive treatment of non-convulsive status epilepticus. Neurocrit. Care 2013;18:216–27.
Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. Anesth. Analg. 2009;109:506–23.
Fürbass F, Herta J, Koren J, Westover MB, Hartmann MM, Gruber A, et al. Monitoring burst suppression in critically ill patients: Multi-centric evaluation of a novel method. Clin. Neurophysiol. 2016;127:2038–46.
Fürbass F, Ossenblok P, Hartmann M, Perko H, Skupch AM, Lindinger G, et al. Prospective multi-center study of an automatic online seizure detection system for epilepsy monitoring units. Clin. Neurophysiol. 2015;126:1124–31.
Gwet KL. Handbook of inter-rater reliability. In: Adv. Anal.. fourth ed. LLC; 2014.
Hartmann MM, Schindler K, Gebbink TA, Gritsch G, Kluge T. PureEEG: Automatic EEG artifact removal for epilepsy monitoring. Neurophysiol. Clin. 2014;44:479–90.
Herta J, Koren J, Fürbass F, Hartmann M, Kluge T, Baumgartner C, et al. Prospective assessment and validation of rhythmic and periodic pattern detection in NeuroTrend: a new approach for screening continuous EEG in the intensive care unit. Epilepsy Behav. 2015;49:273–9.
Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. J. Clin. Neurophysiol. 2013;30:1–27.
Husain AM, Horn GJ, Jacobson MP. Non-convulsive status epilepticus: usefulness of clinical features in selecting patients for urgent EEG. J. Neurol. Neurosurg. Psychiatr. 2003;74:189–91.
Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. Epilepsia 2006;47:41–5.
Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J. Clin. Neurophysiol. 1999;16:341–52.
Koren J, Herta J, Draschtak S, Pötzl G, Pirker S, Fürbass F, et al. Prediction of rhythmic and periodic EEG patterns and seizures on continuous EEG with early epileptiform discharges. Epilepsy Behav. 2015;49:286–9.
Ney JP, van der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005–2009. Neurology 2013;81:2002–8.
Sutter R, Stevens RD, Kaplan PW. Continuous electroencephalographic monitoring in critically ill patients: indications, limitations, and strategies. Crit. Care Med. 2013;41:1124–32.
Synek VM, Synek BJ. Theta pattern coma, a variant of alpha pattern coma. Clin. Electroencephalogr. 1984;15:116–21.
Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J. Neurosurg. 1999;91:750–60.
Westmoreland BF, Klass DW, Sharbrough FW, Reagan TJ. Alpha-coma. Electroencephalographic, clinical, pathologic, and etiologic correlations. Arch. Neurol. 1975;32:713–8.
Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 1996;47:83–9.