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ORIGINAL WORK

Quantitative Infrared Pupillometry in Nonconvulsive Status Epilepticus

Jana Godau[1,2*], Claudia Bierwirth[1], Johannes Rösche[1,3] and Julian Bösel[1]

Abstract

Background: Nonconvulsive status epilepticus (NCSE) is a frequent disorder in neurocritical care and diagnosing it can be challenging. NCSE patients often show altered pupil function, but nature and extent may vary. Infrared pupillometry allows detection of subtle changes of pupil function. The neurological pupil index (NPi) is considered a surrogate marker of global pupil function which is supposed to be independent of absolute parameters such as the pupil diameter.

Objective: Cross-sectional observational study to assess whether NPi is altered in NCSE.

Methods: 128 consecutive adult emergency patients who had experienced a suspected seizure, have not reached their prior functional level regarding level of consciousness, mental status or focal deficits, had no obvious clinical signs of status epilepticus and had an EEG indication as determined by the treating clinician for exclusion of NCSE were examined by routine EEG and pupillometry. Exclusion criteria were ocular comorbidity ($n = 21$) and poor EEG quality ($n = 4$). Pupillometry was performed once directly before the beginning of EEG recording. NCSE diagnosis (no NCSE, possible NCSE and confirmed NCSE) was established according to Salzburg consensus criteria blinded to pupillometry results. Group comparison was performed for right NPi, left NPi, lowest NPi of both sides (minNPi) and the absolute difference of both sides (diffNPi) applying non-parametric testing. In post-hoc analysis, receiver operating characteristics (ROC) of NCSE diagnosis (combined confirmed NCSE and possible NCSE) were performed for minNPi and diffNPi.

Results: From 103 patients included in the final analysis, 5 (4.9%) had confirmed NCSE, 7 (6.8%) had possible NCSE. Right NPi ($p = 0.002$), left NPi ($p < 0.001$) and minNPi ($p < 0.001$) were significantly lower in "confirmed NCSE" and "possible NCSE" compared to "no NCSE"; diffNPi was significantly higher in "confirmed NCSE" and "possible NCSE" compared to "no NCSE" ($p < 0.001$). There was no significant difference of minNPi and diffNPi between "confirmed NCSE" and "possible NCSE". ROC analysis showed an optimal cut-off of minNPi for NCSE diagnosis of 4.0 (AUC = 0.93, 95% CI 0.86–0.99). Optimal ROC analysis cut-off of diffNPi for NCSE diagnosis was 0.2 (AUC = 0.89, 95% CI 0.80–0.99).

Conclusions: NPi was significantly reduced and the difference between left and right NPi was significantly higher in confirmed NCSE. An NPi < 4.0 on either side as well as an NPi difference of both sides > 0.2 may be potential indicators of NCSE. Infrared pupillometry may be a helpful diagnostic tool in the assessment of NCSE and should be studied further in larger populations.

Keywords: Status epilepticus, Pupillometry, Neurological pupil index

Introduction

Diagnosing nonconvulsive status epilepticus (NCSE) can be challenging, particularly in a busy emergency department or in the neurocritical care unit. Especially in elderly and critically ill patients NCSE can be

*Correspondence: jana.godau@klinikum-kassel.de
[1] Department of Neurology, Klinikum Kassel, Mönchebergstr. 41-43, 34125 Kassel, Germany
Full list of author information is available at the end of the article

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underdiagnosed [1, 2]. According to the Salzburg consensus criteria (SCC), NCSE diagnosis is established by combining clinical features, electroencephalography (EEG) findings and response to antiepileptic drugs [3]. These criteria differentiate NCSE by likelihood (no NCSE, possible NCSE, confirmed NCSE), reflecting some diagnostic uncertainty [4].

Non-invasive infrared pupillometry allows a standardized quick and reliable quantitative assessment of pupil function including diameter, constriction and dilation velocity and latency of pupillary light response [5]. The pupillometer is a portable handheld device for bedside application. In some neurocritical care settings, pupillometry has successfully replaced conventional pupil testing [5–7]. The examination can be performed without any specific training by doctors and nurses alike, does not take longer than conventional pupil testing with a penlight and is less affected by external factors such ambient light conditions [6]. Inter-rater reliability was shown to be higher for pupillometry than for conventional pupil testing [8].

The neurological pupil index (NPi) forms a surrogate marker of global pupil function, which is thought to be rather independent of absolute parameters such as the pupil diameter. NPi can reach values from 0 to 5, with NPi values of 3.0 and below indicating a substantially impaired global neurological pupil function [9]. Studies have shown the value of pupillometry for prognostication after cardiac arrest [10–12] and for detection of a critical increase in intracranial pressure in traumatic brain injury [13] and other conditions [14, 15]. Alterations of pupil function as measured by pupillometry have also been related to delirium after surgery [16], depression [17, 18], migraneous photophobia [19], preclinical Alzheimer's disease [20, 21], dopaminergic stimulation in Parkinson's disease [22] and overactive bladder disease [23]. Mostly, these changes were attributed to functional alterations of adrenergic and cholinergic brain activity [24].

The rather frequent presence of gastrointestinal, cardiac and respiratory symptoms during seizures indicate a relation between epileptic activity and cholinergic as well as adrenergic autonomous function. Widened or slowly reactive pupils can be a neurological sign of seizure activity [25, 26]. However, changes can be subtle, clinical assessment using a penlight is rather subjective and may be substantially biased by several factors including ambient light, duration, brightness and direction of the light impulse, administered drugs and the experience of the examiner [5]. So far, there is no systematic evidence for altered pupillary light response as a typical clinical feature of NCSE [27]. Recently, however, a pupillometry study in patients undergoing electroconvulsive therapy (ECT) showed that an altered pupil response was related to sufficient ECT induction [25, 28]. These results suggest that pupillometry may allow detection of subtle changes of pupillary function related to EEG seizure activity. In this study, we aimed to assess the NPi as a surrogate parameter for global pupil function measured by infrared pupillometry in a clinical emergency setting of NCSE.

Methods

In this prospective cross-sectional observational study 128 consecutive patients presenting in the emergency department from January-December 2019 after a suspected epileptic seizure and not having reached their prior functional level were examined by routine EEG and infrared pupillometry (NPI®-200, NeurOptics, Laguna Hills, CA). EEG and NPi assessment were performed in the emergency department with standard ambient lighting conditions (non-dimmed ceiling lights, no daylight, no additional light sources). Pupillometry was performed as a single assessment immediately prior to the beginning of the EEG recording. NCSE diagnosis was established according to the SCC by an expert (JR) who was blinded to the pupillometry results.

Inclusion criteria were: (1) age $\geq$ 18 years, (2) epileptic seizure according to episode description, (3) no clear clinical signs of status epilepticus—including motor convulsions—prompting immediate medical intervention and (4) EEG indication for NCSE exclusion as determined by the treating clinician. According to local practice guidelines, NCSE exclusion EEG will be indicated whenever patients have not reached their prior functional level at the time of admission to establish early discrimination of a prolonged postictal interval from NCSE. Conditions may include an impaired level of consciousness, altered mental status or acute persisting neurological deficits such as aphasia. Prior to EEG, all patients will have received non-contrast head CT and in case of impaired consciousness CT angiography of intracranial vessels to exclude acute life-threatening brain lesions (i.e., due to ICP increase) and basilar artery thrombosis. Patients with any such lesion were not included in the study.

Exclusion criteria were: (a) prior ocular surgery or ocular disease (e.g., glaucoma) which may impact pupillometry results and (b) poor EEG quality which does not allow diagnosis of NCSE according to SCC.

For statistical analysis, we used IBM SPSS Statistics 25.0 (IBM, Armonk, NY). Descriptive data are given either as median and range or as percentages. Regarding NPi, we evaluated the NPi of the right and left side separately as well as the lower NPi of both sides (minNPi) and the absolute difference of both sides (diffNPi). NCSE group comparison was performed using Kruskal–Wallis test with post-hoc Mann–Whitney *U*-Test. Results were assumed to be significant at $p < 0.05$. Bonferroni

correction for multiple comparisons was applied to post-hoc tests.

Secondary analysis focused on minNPi and diffNPi. Receiver operating characteristics (ROC) analysis were performed to assess for a minNPi and diffNPi cut-off differentiating NCSE and non-NCSE patients. For this part of the analysis, patients with possible and confirmed NCSE were combined to one group.

Results

Overall, 25 patients were excluded, four because of poor EEG quality and 21 because of ocular comorbidity. 103 patients were included in the final analysis. Median age was 69 (18–95) years, 49.5% were female. Five patients (4.9%) were diagnosed with confirmed NCSE, seven patients (6.8%) with possible NCSE. All patients in the possible NCSE group were female. Age was comparable between groups and did not correlate with NPi. Prehospital benzodiazepines had been administered to 50.5% without group differences. None of the patients had received other sedatives, analgesia or antiepileptic drugs for acute treatment prior to EEG, no patient had vasopressors and no patient was intubated. Median Glasgow Coma Scale (GCS) upon admission was 9 (3–15). Median time from seizure onset to the beginning of EEG recording was 94 (43–244) minutes. Mean NPi was 4.50 ± 0.36 for the right and 4.51 ± 0.31 for the left side, mean difference of both sides was 0.16 ± 0.20.

Demographics, seizure classification and pupillometry findings for the three groups are shown in Table 1. NPi of the left (Kruskal–Wallis, $p < 0.001$) and of the right side ($p = 0.002$) as well as minNPi ($p < 0.001$) and diffNPi ($p < 0.001$) differed significantly between groups. Subgroup analysis (post-hoc Mann–Whitney *U*-Test, Bonferroni correction for multiple comparisons) showed significant differences of NPi of both sides, minNPi and diffNPi between the "no NCSE" and the "confirmed NCSE" group as well as between the "no NCSE" and the "possible NCSE" group; (see Table 2). Differences between the "possible NCSE" and the "confirmed NCSE" group were not significant after correction for multiple comparisons, however, there was a tendency toward lower minNPi and higher diffNPi in the "confirmed NCSE" group (see Fig. 1). There was no association of NPi, minNPi and diffNPi with demographic parameters and seizure characteristics including prehospital benzodiazepines.

For ROC analysis "possible NCSE" and "confirmed NCSE" were combined to one group. ROC analysis showed an optimal minNPi cut-off at 4.0 with an area under the curve (AUC) of 0.93 (95% confidence interval (CI) 0.86–0.99, Fig. 2a). At this cut-off sensitivity was 66.7%, specificity was 97.8% for NCSE. The false-positive rate (FPR) was 20%, the false-negative rate (FNR) was 33.3%. All false-negatives belonged to the "possible

Table 1 Group characteristics and neurological pupil index

	No NCSE ($n = 91$)	Possible NCSE ($n = 7$)	Confirmed NCSE ($n = 5$)	*p* value
Age (years)	69 (18–95)	77 (60–92)	67 (19–87)	n.s
Sex (female)	45.0%	100%	40.0%	0.02
Seizure type (ILAE)				
Generalized onset	35.2%	42.8%	40%	n.s
Focal onset	40.7%	28.6%	40%	n.s
Unknown onset	34.1%	28.6%	20%	n.s
Seizure etiology (ILAE)				
Acute symptomatic	19.8%	42.9%	20%	n.s
Remote	50.5%	42.9%	60%	n.s
Progressive	23.1%	14.2%	–/–	n.s
Defined electroclinical syndrome	–/–	–/–	20%	n.s
Unclear	6.6%	–/–	–/–	n.s
Known epilepsy (%)	29.7%	28.6%	40%	n.s
Prehospital benzodiazepines (%)	50.5%	42.8%	60.0%	n.s
NPi right	4.6 (3.3–4.9)	4.2 (3.5–4.9)	3.8 (2.9–4.7)	0.002
NPi left	4.6 (4.0–4.9)	4.5 (3.9–4.6)	3.6 (3.3–4.6)	< 0.001
minNPi	4.6 (3.3–4.9)	4.0 (3.5–4.4)	3.5 (2.9–3.9)	< 0.001
diffNPi	0.1 (0–0.7)	0.3 (0.1–1.0)	0.5 (0.4–1.1)	< 0.001

diffNPi absolute difference of left and right NPi, *ILAE* International League Against Epilepsy, *minNPi* lowest value of left and right NPi, *NCSE* non-convulsive status epilepticus, *NPi* neurological pupil index

Table 2 Clinical data of patients diagnosed with non-convulsive status epilepticus

Patient	1	2	3	4	5	6	7
Age	87	66	19	67	76	60	77
Sex	Female	Male	Female	Male	Male	Female	Female
Subgroup	NCSE	NCSE	NCSE	NCSE	NCSE	Possible NCSE[b]	Possible NCSE[b]
Known epilepsy	No	No	Yes	No	Yes	No	No
Prehospital benzodiazepines	Yes	No	Yes	No	Yes	Yes	No
NCSE etiology Axis 1 ILAE 2015	NCSE with coma	Aphasic SE	NCSE with coma	NCSE with coma	Typical absence status	NCSE with impaired consciousness	NCSE with impaired consciousness
NCSE etiology Axis 2 ILAE 2015	Remote	Acute (autoimmune encephalitis)	Remote	Remote	Defined electro-clinical syndrome[a]	Progressive (meningeal carcinomatosis)	Remote
NPi right/left	3.9/4.6	4.7/3.6	3.5/3.9	3.8/3.3	2.9/3.3	3.5/4.1	3.8/4.1
EEG pattern	Right frontotemporal SW	Generalized SW, focus left temporal	Right temporal SW	Generalized SW	Generalized 3/s SW	Right frontotemporal non-evolving LPED	Left hemispheric non-evolving LPED
Matching NPi and EEG pattern	Yes	Yes	Yes	n.a	n.a	Yes	No

ILAE International League Against Epilepsy, *LPED* lateralized periodic epileptiform discharges, *NCSE* non-convulsive status epilepticus, *NPi* neurological pupil index, *SE* status epilepticus, *SW* Spike-wave/sharp wave

[a] Relapsing absence status of later life

[b] Later confirmed NCSE

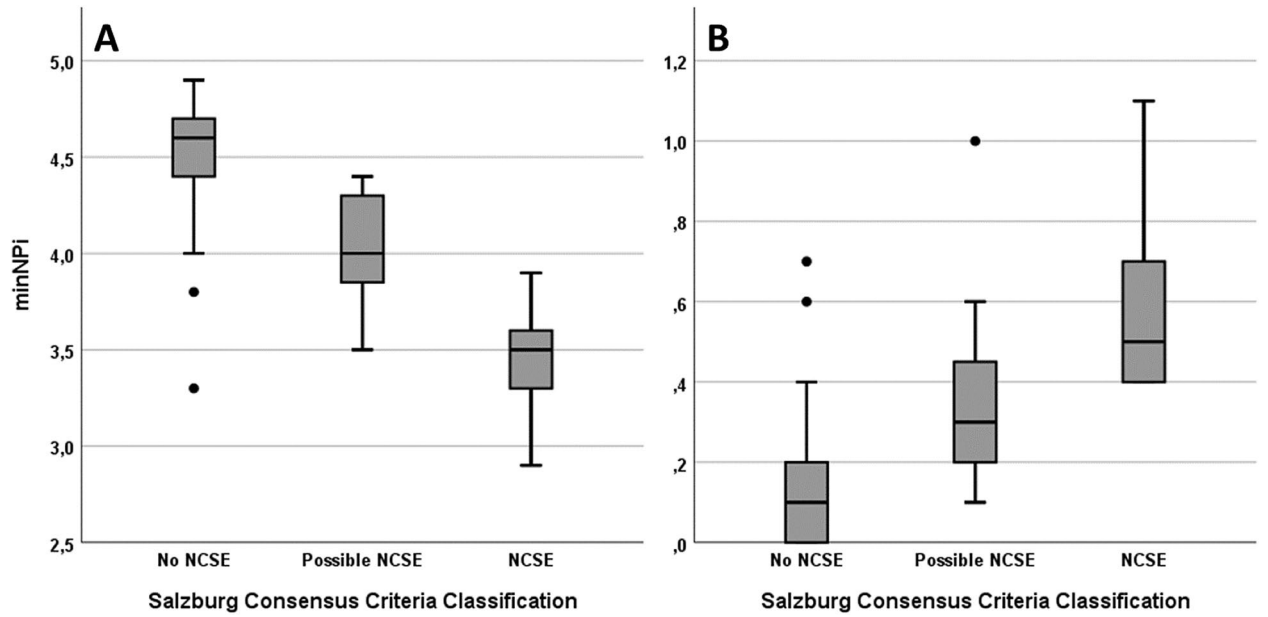

Fig. 1 Neurological pupil index in non-convulsive status epilepticus. **a** Lowest neurological pupil index (NPI) of both Sides (minNPi), **b** absolute side difference of right and left NPi values (diffNPi); NCSE: non-convulsive status epilepticus

NCSE" group, there were no false-negatives in "confirmed NCSE".

Optimal diffNPi cut-off was 0.2 with an AUC of 0.89 (95% CI 0.80–0.99, Fig. 2b). At this cut-off sensitivity was 75.0%, specificity was 91.2%, FPR was 47.0% and FNR

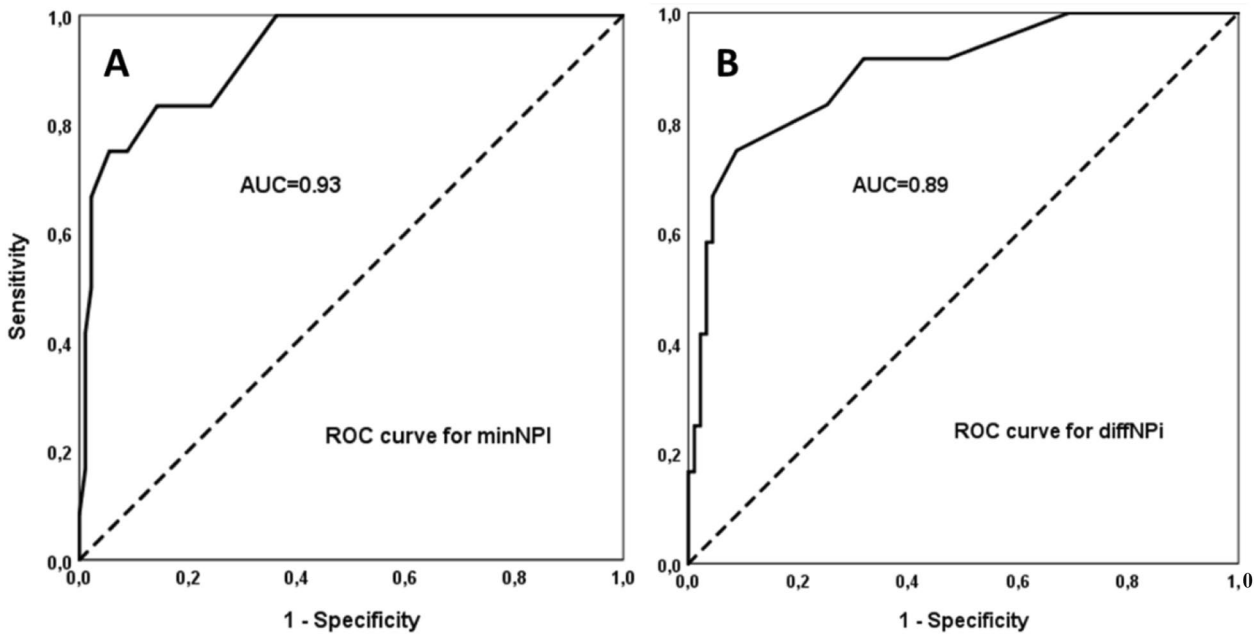

Fig. 2 Receiver operating characteristics for diagnosis of non-convulsive status epilepticus. **a** Lowest neurological pupil index (NPI) of both Sides (minNPi), **b** absolute side difference of right and left NPi values (diffNPi), AUC: area under the curve

was 25.0%. All false-negatives belonged to the "possible NCSE" group, there were no false-negatives in the "confirmed NCSE" group.

In the "possible NCSE" group final diagnosis at hospital discharge was NCSE in two cases; both cases were correctly identified by pupillometry (minNPi 3.5 and 3.8, diffNPi 0.6 and 0.3, respectively). Discharge diagnoses in the other five cases were thalamic stroke, uremic encephalopathy in acute renal failure, septic encephalopathy (2x) and single complex-partial seizure with prolonged postictal phase in severe dementia. Four of these patients were correctly classified by pupillometry, only the dementia patient was false-positive.

More detailed information on the seven patients finally diagnosed with NCSE (including both patients from the "possible NCSE" group finally diagnosed with NCSE) is given in Table 2. In four patients lower NPi and EEG ictal activity lateralized to the same side, in one patient to opposite sides, in two patients no lateralization of EEG ictal activity could be observed.

Discussion

NPi was significantly lower in patients with NCSE and the difference between left and right NPi was significantly higher compared to non-NCSE patients. ROC analysis showed good group discrimination abilities for both minNPi and diffNPi. There were no false-negative findings among the NCSE patients. NPi laterality was consistent with laterality of EEG ictal activity in 80% of the patients. To the best of our knowledge, this is the first prospective systematic investigation of quantitative pupillometry in NCSE.

The prevalence of NCSE in our study cohort was rather low (6.8%), but in line with previous reports [29–33]. However, comparability is limited since NCSE diagnostic criteria have changed over time, some studies focused on emergency patients with altered mental status or coma and others did not differentiate NCSE from simple seizures or postictal phenomena.

All patients diagnosed with NCSE according to Salzburg EEG consensus criteria were correctly identified by pupillometry. Interestingly, six of the seven patients classified as "possible NCSE" were correctly grouped by NPi at the time of initial EEG according to the final diagnosis at discharge (NCSE vs. no NCSE). These results suggest that infrared pupillometry may complement the clinical diagnostic approach to NCSE. It may constitute an objective marker of pupillary dysfunction as a subtle neurological NCSE feature. This may become especially interesting for classification of uncertain cases after initial EEG ("possible NCSE") as well as for scenarios when EEG is not available. Its potential as a diagnostic marker may be limited, given the mostly normal NPi values compared to previously suggested cut-offs even in NCSE

patients and the high FPR of 20% for minNPi and 47% of diffNPi in our study cohort.

No patient had an obvious alternate explanation for NPi and diffNPi alterations, such as acute severe brain injury or ocular comorbidity. However, not all potential confounders could be addressed in this study. This includes for example disorders such as dementia, diabetes and depression and medication. Additionally, pupillary response may be altered by a number of factors, such as cognitive state, attention, arousal state and even mood [16, 20, 34–40]. None of these studies evaluated NPi as a global functional marker. However, one may speculate that NPi can also be influenced by these factors, which are most likely altered to some degree in postictal patients investigated in this study.

This raises the question whether NCSE was causative of the NPi changes observed in our cohort. The finding that NPi laterality matched the laterality of EEG ictal activity in 4 out of 5 patients may support the idea of such a relationship. The mathematical algorithm underlying NPi calculation, however, is proprietary information, which limits considerations about the pathophysiology of NPi changes in NCSE. Additionally, the origin of alterations of pupillary function in status epilepticus is not yet fully understood. Transient changes of pupil diameter have been described as common features in generalized and partial seizures, including ictal unilateral or bilateral mydriasis as well as miosis [41]. Those changes have been attributed to transient functional alterations of the central autonomic network (CAN) [42]. However, it is still a subject of discussion, whether these are caused either by CAN activation or inhibition and whether the main drive comes from the sympathetic or parasympathetic system [42–44]. All these mechanisms may play a role, depending on localization and spreading of brain ictal activity. This is supported by some reports on the rare phenomenon of NCSE pupillary hippus in association with focal EEG ictal and interictal activity in different brain regions [26, 43, 45, 46]. Overall, there is consensus that brain ictal activity in frontal, temporal, parietal, occipital and limbic areas may variably alter pupil function. Therefore, absolute pupil diameter and penlight reactivity to light may not be helpful clinical markers. NPi forms a surrogate parameter of global pupil function, irrespective of pupil diameter and possibly also irrespective of the underlying mechanism of pupillary dysfunction. Therefore, a causative relationship between NPi and NCSE seems possible, but has not been proven so far. Additionally, its clinical relevance compared to other potential sources of NPi alterations remains unclear.

Although the pathomechanism underlying NPi changes in NCSE needs further elaboration, results of this study support pupillometry as a potentially promising add-on bedside diagnostic tool for NCSE. As the examination does not take longer than a conventional pupil exam, is reliable, easy to perform and provides additional and unique information, it could potentially replace the conventional pupil exam in some acute and critical care settings for screening purposes. Early initiation of NSCE treatment is a main predictor for a beneficial outcome [47]. Detection of lowered NPi in patients with altered mental status may prompt early EEG as well as immediate treatment even when EEG is not available [29]. Potentially, pupillometry may also help in the management of NCSE patients on the ICU preventing unnecessary treatment, i.e., during the wake-up phase after induced anaesthesia when non-specific subtle motor phenomena and periodic EEG patterns may impede diagnosis of ongoing NCSE [48–50].

Limitations

The limitation of NCSE diagnostic certainty as reflected by the definition of NCSE likelihoods in the gold standard criteria may also generally limit the evaluation of newer diagnostic tools such as pupillometry. Our study cohort reflects a general cohort of patients seeking emergency treatment after a suspected seizure. Therefore, although consistent with previous studies on NCSE prevalence in emergency settings, the number of NCSE cases was overall rather small. We decided for this design since it reflects a regular clinical setting and thus minimizes the risk of an overestimation of NPi diagnostic potential for a relatively rare condition in the presence of many potential confounders.

Consistent with previous pupillometry studies we excluded all patients with prior eye surgery and ocular disease from analysis, almost one fifth of our study cohort. This may constitute a limitation of the method itself as the impact of prior eye surgery and ocular disease on NPi are rather unknown.

Moreover, it needs to be considered that NPi changes are certainly not disease specific, alterations have been reported for various conditions, including-among others-mild traumatic brain injury [51] and even physiological changes of intracranial pressure in healthy subjects undergoing head-down tilt test [15]. Mean normal NPi in neurocritical care cohorts ranged from 4.1 to 4.3 in previous studies, which is lower than in our cohort [52]. This may reflect differences in cohort characteristics since our cohort constitutes an emergency cohort rather than a critical care cohort. Additionally, severe acute brain lesions were excluded in all patients prior to inclusion. NPi differences between the cohorts may partially be explained by differences regarding severity of underlying brain lesions as well as by analgesia and sedation. Moreover, differences in ambient lighting conditions (i.e., the

absence of daylight in our study) may have contributed to the differences.

Furthermore, group differences in our study were much less pronounced than reported in previous studies on traumatic brain injury [13, 15, 53] and hypoxic ischemic encephalopathy after cardiac arrest [10–12], which may be reasonable considering a functional impairment of pupil function in NCSE rather than an acute structural brain lesion causing pupil dysfunction. Optimal cut-offs for NCSE group differentiation were 4.0 for minNPi and 0.2 for diffNPi in our cohort, which would have been considered normal values in the named studies proposing much lower NPi cut-offs of 3.0 and 2.0, respectively. Therefore, the value of pupillometry for detection of NCSE in critically ill patients with severe brain damage may be limited. On the other hand, serial NPi assessment could potentially show NPi fluctuations related to non-convulsive seizure activity even in these patients.

Conclusion

In summary, non-invasive infrared pupillometry may potentially be a helpful add-on clinical examination in the diagnostic approach to NCSE. An NPi < 4.0 on either side may be considered a potential subtle clinical feature in NCSE as well as an NPi difference of both sides > 0.2. Our data should encourage further research on the value of pupillometry for diagnosis and management of NCSE.

Author details
[1] Department of Neurology, Klinikum Kassel, Mönchebergstr. 41-43, 34125 Kassel, Germany. [2] Emergency Department, Klinikum Kassel, Kassel, Germany. [3] Department of Neurology, University of Rostock, Rostock, Germany.

Author contributions
Authorship requirements have been met by all authors. JG, JR and JB designed the study. JG, JR and CB participated in data acquisition. JG wrote up the first draft of the manuscript. All authors took part in data analysis, interpretation and critical review of the manuscript. The final draft of the manuscript was approved by all authors.

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Conflicts of interest
JG has nothing to disclose. CB has nothing to disclose. JR reports personal fees from Eisai GmbH, outside the submitted work. JB reports personal fees from Medtronic, personal fees from Boehringer Ingelheim, personal fees from Zoll and grants from PCORI, all outside the submitted work.

Ethical Approval/Informed Consent
The study was performed in adherence to ethical guidelines. Ethical approval including a formal consent waiver for observational pupillometry was granted by the Hesse Medical Association Ethical Board.

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