Electrodermal activity response during seizures: A systematic review and meta-analysis

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1. Introduction

Epilepsy is a common neurological disorder which can result in significant impairment to quality of life [1,2] and increased premature mortality [3,4]. This is particularly true among drug-resistant subjects who do not respond to anti-seizure medications and continue to experience seizures. Among deaths directly attributable to epilepsy or seizures, sudden unexpected death in epilepsy (SUDEP) is the most common cause [5]. In the recent years, there have been extensive developments in wearable devices aimed at seizure detection [6] and risk assessment [7]. Among other applications, a continuous monitoring of seizures may help at delineating individual risk of SUDEP and at tracking the evolution of factors that may predispose to SUDEP over time. One promising parameter used for this aim is electrodermal activity (EDA).

Electrodermal activity was first described many years ago [8], but has attracted increasing interest in the last few decades [8,9]. Electrodermal activity theoretically represents purely sympathetic activity from eccrine sweat glands on the skin [9]. It can be divided into tonic and phasic components; the tonic component refers to long-term fluctuations in EDA and is characterized by the skin conductance level, whereas the phasic response represents brief changes in EDA elicited by external/internal stimuli and measured as skin conductance response or galvanic skin response [10]. Seizures can trigger an EDA response through sweating causing reduced skin resistance [11]. The highest electrodermal responses are traditionally obtained from the face, palms, and soles. However, the wrists have also been reported to show good EDA responses while providing the added benefit of convenience for long-term outpatient recording through the use of wrist-worn devices [12]. The central control of EDA is still not fully understood, but appears to involve multiple brain areas, including the hypothalamus and amygdala among others, with both ipsilateral and contralateral control depending on the brain region involved [13]. It is thought that EDA responses during seizures arise as a result of seizure activation of the central autonomic network [14,15], this occurs when the seizure onset involves or spreads to limbic system.
2. Methods

The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the Cochrane Handbook guidelines [21,22].

2.1. Inclusion and exclusion criteria

All original research studies (cohort, case-control, case series, case report) assessing concurrent EEG and EDA during the pre-ictal, ictal, or postictal period in both children and adults were considered for inclusion. Studies which only assessed psychogenic nonepileptic seizures (PNES), neonatal seizures or interictal periods were excluded. Further, any studies which did not include the total number of seizures and number of seizures with EDA response were excluded for meta-analysis but included for qualitative analysis. A minimum number of participants was considered in the inclusion/exclusion criteria for the meta-analysis; however, all the studies included in the meta-analysis had more than five participants.

2.2. Search strategy

A systematic search was performed to identify all relevant published and unpublished articles. No language or time restrictions were applied. The search was performed on Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL), and included articles up to the 29th October 2021. The search strategy for each database was performed based on the Medline search strategy which is reported in Appendix 1. Terms used in the search strategy included: “seizures”, “epilepsy”, “electrodermal activity”, “electrodermal response”, “skin conductance response”, “Galvanic skin response” and “EDA”. In addition, the bibliographies of all related review articles were hand searched for additional relevant articles.

2.3. Data collection and analysis

The titles and abstracts of all articles identified through the database searches and hand search were independently assessed for relevance following removal of duplicates. The full texts of all relevant articles were obtained and screened for fulfillment of inclusion and exclusion criteria. Any doubts regarding inclusion of articles were resolved through discussion. A table was created to extract data from all included studies. The data collected included: study design and setting, number of participants, age, gender, type of epilepsy, type of seizure, type of EEG, definition of seizure onset, method for recording EDA, definition of EDA response, total number of seizures with recorded EDA, number of seizures with pre-ictal or postictal EDA response, and other EDA features recorded in the study.

2.4. Quality assessment

All studies were quality-assessed using a modified standard quality assessment tool (Appendix 2) [1]. This included sample representativeness, assessment of seizures, and EDA and statistical analysis. Studies were given a quality score between 0 and 8.

2.5. Data synthesis and analysis

Studies which reported the total number of seizures and seizures showing an electrodermal response were included for meta-analysis. The ‘metaprop_one’ command in Stata 14.0 was used to estimate the crude incidence rates and the 95% confidence intervals (CI). We expressed the estimates as the number of seizures with EDA response per 100 seizures. We reported the pooled, weighted estimate generated by random effects models. The I² was used to quantify the magnitude of between-study heterogeneity and the Cochrane Q statistic was calculated to determine significance. Publication bias was investigated statistically using Egger’s test. Significance level was established at p < 0.05. As a sensitivity analysis, we planned to repeat the pooling process after the successive removal of studies with a low-quality score (less than 5/8). All analyses were performed using STATA version 14.0 (StatCorp, College Station, TX, U.S.A.).

3. Results

3.1. Study selection and quality assessment

The electronic database search yielded 321 references (Fig. 1). An additional 15 references were identified through hand-searching. After duplicates were removed, the abstracts of 239 references were screened for inclusion. The full texts of 56 articles were assessed for eligibility; of which 37 articles were excluded for one of the following reasons: no EEG data recorded, EDA response not individually assessed, only interictal data reported, duplicated datasets, or non-original research article. Specifically, the Poh et al. study [23] was excluded due to documented overlapping dataset with the Sarkis et al. study [24].

In total, 19 studies were considered eligible for this review and their characteristics are summarized in Table 1. Of the included studies, six were included for meta-analysis [17,18,25–28]. The remaining 13 studies [19,20,29–39] were only considered for qualitative analysis, as they did not report the frequency of seizures with an EDA response.

Quality assessment demonstrated a mean quality score of 4/8 (range 0–7) for all included studies and a mean quality score of 6/8 (range 5–7) for studies included in the meta-analysis. Given all studies included in the meta-analysis scored a minimum of 5 points, the planned sensitivity analysis was not performed. Studies most frequently lost points for sample representativeness and use of validated criteria to assess EDA response. The former was due to all studies being carried out in inpatients with most including only those with severe epilepsy. The latter was due to lack of standardization or clarity in how the EDA response was defined. Several studies lost a point due to small sample size (<20 participants). The smallest sample size for studies included in meta-analysis was 7; for the systematic review the smallest sample size was 1. Please see Appendix 3 for a table summarizing each article’s quality score.
3.2. Summary of characteristics of the studies

The nineteen studies included a total of 550 participants (46% male, 44% female, 10% not recorded), and 1115 recorded seizures. Five studies [28,31,37,40,41] included both adult and pediatric populations, four [19,26,27,29] included only adults, with another six [17,18,20,34,38,39] including only children or young adults. Four studies [30,32,33,35] did not report the age of participants.

Six studies [18,28,31,37–39] included a mixture of genetic and structural/metabolic epilepsies and one study [19] included temporal lobe epilepsies. The remaining twelve studies [17,20,25–27,29,30,32–35] did not report the epilepsy type. Four studies included GTCS and focal seizures (excluding FBTCS) [17,18,27,34] and one included temporal lobe epilepsies. The remaining twelve studies [17,20,25–27,29,30,32–35,37–39] did not report the epilepsy type. Four studies included GTCS and focal seizures (excluding FBTCS) [17,18,27,34]. Two studies included GTCS and FBTCS [25,31]. Three studies included GTCS, FBTCS, and focal seizures [28,29,37]. One study included only focal seizures (excluding FBTCS) [19]. Three studies included only GTCS [26,38,39]. One study included only motor vs non-motor seizures (generalized vs focal unspecified) [32]. One study included [20] only subclinical seizures, and three studies [30,33,36] did not report the seizure type.

Eighteen studies [17–20,25–35,37–39] used scalp EEG, sixteen of which were video-EEG. One study [36] did not report the type of EEG recording used. Eighteen studies [17,18,25–35,37–39] defined seizure onset as the EEG seizure start time. One study [36] did not report a seizure onset definition.

To record the EDA signal, ten studies [18,20,25,30,32–34,37–39] used the Empatica E3 or E4 wristband, three studies [26,31,42] used the Q-sensor Affectiva device, one [35] used Embrace, one [29] used Biopac MP160, one [17] used a local EDA wristband, and three studies [19,28,36] did not report the device used. Two studies [25,31] defined an EDA response as a change of more than two standard deviations from baseline; one study [26] defined it as an increase of more than 0.2 microsiemens lasting more than 2 s; and two [19,27] as more than 60% increase from baseline. Two studies [18,38] defined the EDA response as the difference between the ictal and baseline EDA. Twelve studies [17,20,25–32,35,37–39] did not report a definition for EDA response.

All studies reported an EDA response during seizures. Thirteen studies [17–20,25,26,33,35,37–39,42] reported an EDA increase during the ictal and postictal periods. Five studies [17,18,28,35,37] found that both focal and generalized seizures can elicit an EDA response; however, the response is more pronounced in tonic-clonic seizures (GTCS and FBTCS). Sarkis et al. [31] reported that sympathetic activation was more pronounced in children. Two studies [26,30] reported that EDA can help differentiate between epileptic and nonepileptic seizures. Heldberg et al. [32] found that non-motor seizures showed a delay in EDA response compared to motor seizures. El Atrache et al. [20] found that subclinical seizures elicit an EDA response. Tang et al. [37] found a delayed response time in EDA compared to accelerometry. El Atrache et al. [38] found a positive correlation between increased EDA response and increased postictal generalized EEG suppression (PGES) duration.

Bruno et al. [19] found that EDA onset was preceded by tachycardia, and seizures resulting in bradycardia did not elicit an EDA response. Additionally, the study also found that motor aware seizures did not elicit an EDA response. Interestingly, right focus seizures did not show an EDA response when the wristband was worn on the left side, whereas left focus seizures elicited an EDA response from both wrists.

Fig. 1. PRISMA flow diagram.
## Table 1
Summary of study characteristics.

| Study               | Design and setting | Epilepsy type | Participants (N) | Age group | Gender | Seizure type | EEG type | Definition of seizure onset | EDA recording method | EDA response definition | Total seizures with EDA data | Seizures with pre-ictal EDA changes | Seizures with postictal EDA changes |
|---------------------|--------------------|---------------|------------------|-----------|---------|--------------|----------|----------------------------|----------------------|---------------------------|----------------------------------|--------------------------------------|-----------------------------------|
| Vieluf et al., 2020 | P + I              | 55% structural, 3% genetic, 35% unknown, 7% other | 119, 40 with seizures, 62 epileptic activity without seizure | Peds - mean age 12 | 58M | GTCS + FIAS | vEEG | Mean EDA during seizure minus 24hr baseline mean | Empatica E4 | 59 | 40 (decrease) | NR Increase |
| Hamlin et al., 2021 | P + I              | NR            | 15               | Adults - mean age 36.2 | 7M | Complex partial, partial with secondary generalization, partial motor, PNES | vEEG | Biopac MP160 | NR | 11 | NR | NR Increase |
| Zsom et al., 2019   | P + I              | NR            | 30               | NR | NR | epileptic vs PNES | vEEG | Empatica E4 | NR | 86 | NR | NR Increase |
| Onorati et al., 2017| P + I              | NR            | 69 (peds 24, adults 45) | Peds - mean age 37yrs | 15M | GTCS + FBTCS | vEEG | Empatica E4, + Empatica E3 + MIT iCalm | Increase more than 2 SD from baseline | 55 | NR | 40 (ictal, increase) |
| Sarkis et al., 2015 | P + R + I          | 55% structural/metabolic, 5% genetic, 40% unknown | 20 (279) – 13 adult, 7 peds | Peds and adults - mean age 28.5 (11–67) | 15M | GTCS + FBTCS | vEEG (conventional 10–20 system) | Q-sensor Affectiva | Increase more than 2 SD from baseline | 30 | NR | NR Increase |
| Heldberg et al., 2015| P + I              | NR            | 8                | NR | NR | Motor and non-motor | vEEG | Empatica E3 | NR | 55 | NR | NR Increase |
| Poh et al., 2010    | P + I              | NR            | 7                | Peds and young adults - mean 15.1 | 4M | GTCS + CPS | vEEG (conventional 10–20 system) | Local EDA wristband | NR | 13 (9GTCS, 4CPS) | 13 |
| Reinsberger et al., 2015 | P + I          | NR            | 126 (9 with GTCS) | adults | 7M | GTCS + PNES | EEG | Q-sensor Affectiva | EDA increase of more 0.2microsiemens, lasting > 2seconds | 9GTCS (11 PNES) | 9 GTCS |
| Cogan et al., 2016  | P + I              | NR            | 10               | Adults (21–64 yrs) | 7M | GTCS + CPS | vEEG (conventional 10–20 system) | Q-sensor Affectiva | min 60% increase from baseline | 26 (23CPS, 2FBTCS, 1GTCS) | NR | 19 |
| Thome-Souza et al., 2015 | P + I           | 12.5% genetic, 45.8% metabolic/structural, 41.7% unknown | 48               | Adults and peds (mean 22.1 yrs) | 30M | CPS + GTCS + FBTCS | vEEG | NR | NR | 48 | 38 (19/26 CPS, 8/11 GTCS, 11/11 FBTCS) |
| Villamar et al., 2017| P + I              | NR            | 1                | NR | NR | NR | EEG | Empatica | NR | 6 | Increase | NR Increase |
| Ufongene et al., 2019| P + I              | NR            | 9                | Peds (7–20 yrs) | 4M | GTCS + CPS | vEEG | Empatica E4 | NR | 9 (3CPS, 6GTCS) | NR Increase |
Table 1 (continued)

| Study                             | Design and setting | Epilepsy type | Participants (N) | Age group | Gender | Seizure type | EEG type | Definition of seizure onset | EDA recording method | EDA response definition | Total seizures with EDA data | Seizures with pre-ictal EDA changes | Seizures with post-ictal EDA changes |
|-----------------------------------|--------------------|---------------|------------------|-----------|---------|--------------|----------|----------------------------|----------------------|-----------------------------|-------------------------------|-------------------------------------|-------------------------------------|
| El Atrache et al., 2019           | P + I NR           | 11            | Peds (8 m–18 yrs) | NR        | NR      | Subclinical seizures | NR       | EEG                        | Empatica E4            | NR                          | 17                            | Increase                           | NR Increase                        |
| Zahoor et al., 2020               | P + I NR           | 8             | NR               | NR        | NR      | focal and FBTCS     | vEEG     | EEG                        | Embrace               | NR                          | 949 (only 10 analyzed so far) | NR Increase                         | NR Increase                        |
| Tousserkan et al., 2018           | P + I NR           | 14            | Peds and adults (9–27 yrs) | NR        | NR      | long-term EEG       | EEG      | NR                        | NR                   | NR                          | 27                            | NR Increase                         | NR Increase                        |
| Tang et al., 2021                 | P + I              | 94            | Peds and adults (median 9.9 yrs, range 27) | 54M       | 9       | 9 seizure types, Inc generalized and focal onset, subclinical, impaired awareness etc | vEEG (conventional 10–20 system) | EEG                        | Empatica E4            | NR                          | 548                            | NR Increase                         | NR Increase                        |
| El Atrache et al., 2021           | P + I              | 36.7% unknown, 37% structural, 14% genetic, 3% infectious, 2% metabolic, 1% immune | 334 (30 met inclusion criteria) | 14F       | GTCS | vEEG (conventional 10–20 system) | EEG      | lctal EDA minus baseline EDA | Ematica E4 | 53                           | NR                            | NR Increase                         | NR Increase                        |
| Bruno et al., 2021                | P + I              | 58% temporal lobe epilepsy | 51 (27 had seizures) | Adults | 8M, 5F | Focal – 8 motor with impaired awareness, 5 motor aware | vEEG | EEG                        | NR - wrist | 60% increase from baseline | 53                           | NR Increase                         | 0/29 for motor aware, 16/18 left focus impaired awareness, 0/5 right focus impaired awareness |
| Vieluf et al., 2021               | P + I              | lesional, encephalitis, Tuberous sclerosis, MCA stroke, Immune, Unknown, Lennox Gastaut, metabolic | 220 (21 included in final study) | Children - mean age 10 | 11F | GTCS | vEEG | EEG                        | Ematica E4 | NR                          | NR                            | NR Increase                         | NR Increase                        |

Abbreviations:
P – Prospective; I – inpatient; R – retrospective; GTCS – generalized tonic-clonic seizure; FBTCS – focal to bilateral tonic-clonic seizure; CPS – complex partial seizure; vEEG – video-electroencephalogram; FIAS – focal impaired awareness seizure; PNES – psychogenic nonepileptic seizure; SD – standard deviation; NR – not recorded; EDA – electrodermal activity.
Three studies [18,20,33] reported pre-ictal EDA changes during seizures. Pre-ictal EDA was defined as the 30 min prior to electrographic seizure onset by one study [18] and as the 5 min prior to electrographic seizure onset by a second study [20]. The third study did not report a definition for pre-ictal period [33]. Two studies [20,33] found an increase in pre-ictal EDA, whereas one study [18] found a decrease in pre-ictal EDA in 40 out of 59 seizures. Four studies [25,27,29,36] found that EDA analysis can improve seizure detection mechanisms.

### 3.3. Meta-analysis

Six studies were considered eligible for meta-analysis [17,18,25,26,28,42]. The pooled incidence of EDA response during seizures was 82 per 100 seizures (95% CI 70–91) (Fig. 2). $I^2$ test was 67.18% suggesting significant inter-study heterogeneity. Cochran Q was statistically significant ($p = 0.0002$). Egger’s test was significant ($p = 0.02$) suggesting possible publication bias.

### 4. Discussion

Our systematic review and meta-analysis indicated that a peri-ictal EDA response is present during both focal and generalized seizures, and that the response is higher and longer lasting in tonic-clonic seizures (GTCS and FBTCS) [17,18,25,35]. These results highlight the potential usefulness of EDA as a biomarker of sympathetic overactivation during seizures and its potential use for the detection of different seizure types. However, extensive further research is required to determine which factors can influence this response.

Heldberg et al. [32] found that both motor and non-motor seizures could elicit a detectable EDA response, albeit this again was more pronounced in motor seizures. Bruno et al. [19] found that motor aware seizures did not elicit a response. This could suggest that awareness state during seizures rather than motor vs non-motor seizures also has an impact on the EDA response. In addition, Bruno et al. [19] showed that wearing the EDA sensor on the left did not detect right focus seizures, but left focus seizures were detected with the EDA sensor on either wrist, implying that seizure laterality might have an effect on sympathetic response. All of the above suggest that multiple factors can play a role in the variability of the EDA response, and further research is needed to better understand the ideal seizure target for an optimal seizure detection based on this signal.

Sarkis et al. [31] found that increased sympathetic activation led to more prolonged PGES. This is supported by El Atrache et al. [38] who also found increased EDA response postictally correlated with longer PGES. A review by Rajakulendran and Nashef [43] found a correlation between longer PGES duration and increased risk of SUDEP, particularly in PGES lasting longer than 50 s. Therefore, further investigating sympathetic activation through EDA during seizures could potentially allow individual SUDEP risk estimation.

Sarkis et al. also noted that children tended to have stronger sympathetic responses with longer and more pronounced EDA rises during the postictal period; however, they had shorter PGES than adults. Interestingly, SUDEP occurs less commonly among children as compared with adults [44,45] and further studies assessing how age affects the occurrence of seizure-related autonomic responses are needed to clarify these findings.

Tang et al. [37] showed a delayed EDA response in seizure detection compared to accelerometry. This is supported by the findings of Bruno et al. [19] demonstrating a common evolution pattern (tachycardia followed by motor manifestations followed by EDA) in seizure manifestations. Taking into account the temporal relationship of different autonomic and motor components may potentially improve the accuracy of detection algorithms.

Another important phenomenon is pre-ictal EDA alteration. Vieluf et al. [18] found reduced EDA during the pre-ictal period in 40 out of 59 seizures. However, El Atrache et al. [20] and Villamar et al. [33] found increased pre-ictal EDA. Detection of EDA prior to seizure onset could potentially increase patients’ safety.

### Table 1: Meta-analysis Results

| Study             | EDA (95% CI)     | Weight |
|-------------------|------------------|--------|
| Vieluf et al., 2020 | 0.88 (0.80, 0.95) | 20.94  |
| Overheid et al., 2017 | 0.79 (0.69, 0.89) | 30.62  |
| Pohl et al., 2010  | 1.00 (0.97, 1.03) | 12.10  |
| Reindelberger et al., 2015 | 1.00 (0.97, 1.03) | 8.84   |
| Logan et al., 2016  | 0.73 (0.64, 0.82) | 18.93  |
| Thome-Grais et al., 2015 | 0.79 (0.66, 0.88) | 18.97  |
| Overall ($I^2 = 67.24\%$, $p = 0.0005$) | 0.82 (0.70, 0.95) | 100.00 |

Fig. 2. Cumulative incidence of EDA response during seizures.
by reducing the risk of injuries and the time required to summon help. Nonetheless, given the limited and contradicting research available, further extensive research is required to assess pre-ictal changes in EDA.

Finally, EDA appears to be a useful method to differentiate between epileptic and nonepileptic seizures [26,30]. This could have a significant impact on the management of patients with mixed picture conditions, potentially preventing overtreatment and the associated higher risk of drug-related side effects. At the other end of the spectrum, the presence of a significant increase in EDA during subclinical seizures [20] may prevent undertreatment and suboptimal cognitive performances [46–48].

Overall, this review findings support the use of EDA in seizure-detection algorithms, and indicate enhanced accuracy of seizure detection [25,27,29,49]. A more accurate estimate of seizure frequency would enable a better pharmacological management and a prompter response in acute scenarios, potentially reducing the risk of negative outcomes.

There are several limitations to this review. The main limitation is the small number of papers included, which prevented the assessment of factors influencing the EDA response. A better understanding of the different factors which can alter the EDA response could potentially allow the development of personalized thresholds for individual patients.

In addition, the definition of an EDA response was variable across studies and most studies did not define an EDA response threshold, which could account for variability in results. Not to mention that the use of different EDA definitions between studies means the results may not be comparable. From the meta-analysis, only 3 of the included studies provided a definition for EDA. Of these, the two that defined EDA as a 60% increase from baseline and as 2 standard deviations increase from baseline showed similar response rates, but the study which used an increase of >0.2 microsiemens for >2 s from baseline had a higher response rate. A standardized definition of EDA response, including both amplitude and duration criteria, is needed to increase the reliability and comparability of study results.

Another important limitation to consider is that a significant proportion of studies included in this systematic review were from the same research group, which could mean certain measurements are repeated. To reduce this risk, the authors of articles which were considered at high risk of repetitive samples (e.g., same lab, same year publications) were emailed to confirm this. If the authors confirmed repetitive samples or if no reply was obtained from the authors, the conflicting studies were excluded from the review.

Moreover, although the studies included for meta-analysis were independent from each other, most of the individual studies included more than one seizure from at least one participant. This could not be accounted for statistically which could have influenced the results.

Furthermore, the studies included in this review were carried out in controlled conditions and on hospitalized patients, making it difficult to evaluate the applicability of these findings in the ambulatory settings and on subjects performing daily activities.

5. Conclusion

An EDA response appears to be present in multiple seizure types with an estimated incidence of 82 per 100 seizures. The response is more pronounced in tonic-clonic seizures (GTCS and FBTCs). This is detectable via wearable devices and can be applied in seizure detection algorithms. However, further research is needed to better evaluate which factors influence this response. For example, how does epilepsy type, seizure type, and laterality affect the response? A more in depth understanding of the different factors which alter EDA response could allow more individualized thresholds for patients. Further future directions could also investigate pre-ictal EDA changes. Although there is limited evidence in the literature for pre-ictal changes, if these are indeed present it could make a significant impact in preventing patient harm through earlier notification.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108864.

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