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Predictive Power of Interictal Epileptiform Discharges in Fitness-to-Drive Evaluation

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Glossary: IEDs, interictal epileptiform discharges; RT, reaction times; miss/crash, missed reactions or crashes; 95%-CI, 95% Confidence Interval; 10-90%-IPR, 10-90% interpercentile range; Gen typ, generalized typical (IEDs); Gen atyp, generalized atypical (IEDs).

Abstract

Background: This study aimed to evaluate and predict the effects of interictal epileptiform discharges (IEDs) on driving ability using simple reaction tests and a driving simulator.

Methods: Patients with various epilepsies were evaluated with simultaneous EEGs during their response to visual stimuli in a single-flash test, a car-driving videogame, and a realistic driving simulator. Reaction times (RT) and missed reactions or crashes (miss/crash) during normal EEG and IEDs were measured. IEDs, as considered here, were a series of epileptiform potentials (>1 potential) and were classified as generalized typical, generalized atypical, or focal. RT and miss/crash in relation to IED type, duration, and test type were analyzed. RT-prolongation, miss/crash probability, and odds ratio of miss/crash due to IEDs were calculated.

Results: Generalized typical IEDs prolonged RT by 164ms, compared to generalized atypical IEDs (77.0ms) and focal IEDs (48.0ms) ($p<0.01$). Generalized typical IEDs had a session miss/crash probability of 14.7% compared to a zero median for focal and generalized atypical IEDs ($p<0.01$). Long repetitive bursts of focal IEDs lasting >2s had a 2.6% miss/crash probability$_{IED}$. Cumulated miss/crash probability could be predicted from RT-prolongation: 90.3ms yielded a 20% miss/crash probability. All tests were non-superior to each other in detecting miss/crash probabilities$_{IED}$ (zero median for all three tests) or RT-prolongations (flash test: 56.4ms, car-driving videogame: 75.5ms, simulator 86.6ms). IEDs increased the odds ratio (OR) of miss/crash in the simulator by 4.9-fold compared to normal EEG. A table of expected RT-prolongations and miss/crash probabilities for IEDs of a given type and duration was created.

Conclusion: IED-associated miss/crash probability and RT-prolongation were comparably well detected by all tests. Long focal IED-bursts carry a low risk, while generalized typical IEDs are the primary cause of miss/crash. We propose a cumulative 20% miss/crash risk at a RT-prolongation of 90.3ms as a clinically relevant IED effect. The IED-associated odds ratio in the simulator approximates the effects of sleepiness or low blood-alcohol level while driving on real roads. A decision aid for fitness-to-drive evaluation was created by providing the expected RT-prolongations and misses/crashes when IEDs of a certain type and duration are detected in routine EEG.

Introduction

Driving a motor vehicle is an important societal skill, be it for adults who drive as a means of transportation or for professional mobility, or for adolescents, who often perceive it as a major step towards maturity.[1] Evaluating the fitness-to-drive becomes relevant, particularly in the elderly,[2] and for people with a medical disorder such as epilepsy. Numerous studies have analyzed the accident risk of persons with epilepsy.[3-13] One consequence has been the development of national and international guidelines that define periods of seizure freedom required to obtain and maintain a driver's license. Opinions diverge on how to best evaluate fitness-to-drive and whether pathological EEG findings should be considered. The focus of the EEG evaluation is on interictal epileptiform discharges (IEDs) which occur between seizures and are typically not perceived by patients nor recognizable by routine clinical observation. Nevertheless, IEDs can have serious consequences given their association with transitory cognitive impairment[14-16] and their prevalence. IEDs can be up to 2000 times more frequent than seizures in temporal lobe epilepsy.[17] Their influence on cognition can be variable. Features that are responsible for the variability of IED effects include IED type, duration, configuration, and amplitude,[18-19] as well as IED location particularly in intracranial EEGs.[20-21] A recent survey of European epileptologists revealed varying opinions on the use of EEG and the consideration of IEDs for fitness-to-drive evaluation.[22] However, there was consensus (>80%) on the need for more research to improve evaluation techniques and for coordination and regulation of best practices for evaluating fitness-to-drive.[22] Existing evaluation techniques include a flash test that is used by several epilepsy centers to examine IED effects on responsiveness. A recent pilot study using a realistic driving simulator demonstrated the feasibility of a simulator to test the effects of generalized epileptiform discharges on driving performance.[19]

We previously characterized the effects of generalized IEDs on reaction time (RT) using a single flash test and a car-driving videogame to support clinicians with objective data in their decision to use EEG outcomes for evaluating fitness-to-drive. We found that IED type and IED duration influenced RT. Specifically, RT-prolongation was greater with increasing IED duration, and generalized typical ("well-organized") IEDs prolonged RTs more than generalized atypical IEDs ("other type") or generalized sharp theta activity.[23] We then validated these IED effects on RTs.[24] Focal IED-bursts had the weakest effect on RT-prolongation while generalized typical IEDs showed RT-prolongations between 105-123 ms. Crashes in the car-driving videogame and performance lapses in the flash test indicated test errors. IEDs increased the probability of crashes and lapses, but the higher test error rate could not be explained by a linear increase in RT during IEDs. We showed that the number of different antiseizure medications taken by the patient increasingly slowed responsiveness, but it was the IEDs that correlated with RT-prolongation and test errors.[24]

Despite the wealth of knowledge about the effect of IEDs on cognition, it remains unclear how this knowledge can be applied in a standardized manner to the evaluation of fitness-to-drive and how the IED effects can be translated to real-world situations on the road.

Our study aimed to (1) consolidate the knowledge about IEDs that affect a person's fitness-to-drive; (2) clarify the applicability of simple tests and a realistic driving simulator to study missed reactions or crashes and RT-prolongation; (3) determine the predictability of RT-prolongation with respect to the likelihood of a missed reaction or crash; (4) translate the IED-associated relative risk in the laboratory simulator to the real-road crash risk from the literature and (5) provide clinicians with a decision aid that uses routine EEG to determine which patients are candidates for fitness-to-drive testing or, if tests are not available, to identify potentially clinically relevant IEDs based on expected RT-prolongations and misses/crashes.

Methods

Reaction tests

Effects of IEDs were studied using a flash test, a car-driving videogame (hereafter abbreviated as car test), and a realistic driving simulator (simulator). During each test, a scalp EEG was recorded (figure 1, eMethods).

Interictal epileptiform discharges

EEG recordings were analyzed post-hoc by neurologists (HK, DS, CJ). IEDs (also termed IED-bursts hereafter) were defined on a clinical level as "not recognizable" by regular observation, and on an electrophysiological level as a series of epileptiform potentials (>1 potential) without evolution in frequency (< 1 Hz over the duration of the discharge) and amplitude. Each IED was identified according to its distribution as focal or generalized. A generalized IED was classified as "typical" if it consisted of classically configured spike-waves and/or polyspike-waves with reasonably constant organization and amplitude throughout ("well-organized"[25]). Generalized "atypical" IED consisted of more bluntly configured spike-waves and sharp theta activity and were less well-organized often with variable amplitude over time ("other type"[25]). Focal IEDs were defined independently of their configuration of epileptiform potentials. Examples of the three IED types are shown in eFigure 1. IEDs were examined both at the session level and at the "single" IED-burst level (when sessions were resolved and all individual data pooled). Entire test sessions were labeled as focal, generalized atypical, or generalized typical according to the predominant type of IED in the EEG recording. Single IED-bursts were labeled according to the test session from which they originated.

Study parameters

Each test session consisted of a varying number of stimulus presentations during normal EEG and IEDs in variable order, as determined by IED appearance. For each patient, we recorded: (1) RT [ms], (2) trigger latency [ms], (3) IED duration [ms], (4) missed reactions in the flash test and simulator, and (5) crashes in the car test. A patient could complete one session or multiple sessions (eAppendix 1).

RT was measured during normal EEG ($RT_{normal\ EEG}$) and during IEDs (RT_{IED}). In the flash test, RT was defined as the time between flash triggering and patient reaction, and as time between on-screen obstacle appearance, as recorded by a photo-voltaic sensor, and the patient's response in the car test and simulator, respectively. The trigger latency was defined as the time of appearance of the visual stimulus triggered by the experimentalist relative to IED onset (figure 1A).

The definition of a missed reaction in the flash test and simulator during normal EEG and during IEDs was no response at any latency by the patient. As defined by the programming of the car test, the car would not swerve to avoid the obstacle but would crash into the obstacle unless the patient switched lanes by a button-press within one second. A crash was defined as the collision of the car into the obstacle. For all three tests, the probability of IED-associated missed reactions or crashes (miss/crash probability$_{IED}$) was the number of missed reactions or crashes during IEDs divided by the number of visual stimuli triggered during IEDs in that session. Mean RT-prolongation of a session was mean RT_{IED} minus mean $RT_{normal\ EEG}$ of that test session. RT-prolongation represented the IED-induced deficit on each participant's RT, controlled by their own normal/baseline RT. The reader is referred to eMethods for calculation of the miss/crash probability during normal EEG, miss/crash probability and RT-prolongation due to single IED-bursts, and the cumulative distribution function that related miss/crash probability with RT-prolongation. The total stopping distance in the realistic

driving simulator was investigated as an additional behavioral measure (eMethods, eAppendix 1). Treatment of missing variables and control of confounders is described in eMethods.

Influence of biological or environmental factors on driving performance in the literature and comparison with IEDs

First, we directly compared the increase in RT due to biological/environmental factors with IED-associated RT-prolongation. Second, we compared the percent increase in RT or lane deviation of a vehicle (measured in cm) due to drowsiness, blood-alcohol concentration, or medications/drugs with the percent increase in IED-associated RT-prolongation. Third, we compared the reported odds ratios and relative risk of collisions in a laboratory simulator due to blood alcohol, or of fatal or non-fatal accidents in real-road studies due to drowsiness, or blood alcohol, with the odds ratio and relative risk of IEDs in our simulator.

Statistical analyses

Statistics were calculated with GraphPad Prism 9 and R. Recorded and calculated parameters were given as mean (SD) in eTable 1 and presented as medians with 10-90% interpercentile ranges (10-90%-IPR) in the main text, and as medians with 95%-confidence intervals (95%-CI) in the figures, eFigures and eTable 2. Group-wise comparisons were done by paired or unpaired non-parametric tests, as indicated. Odds ratios and relative risk were calculated using contingency tables, tested with the chi-square test, and given as values with 95%-CI. eTable 3 reports all analyses in terms of group size or number of values, whether the data were paired or unpaired, statistical test used, minimum and maximum values, range, median, 10th percentile, 90th percentile, and 10-90% interpercentile range. Results were significant at corrected p two-tailed < 0.05.

Standard Protocol Approvals, Registrations, and Patient Consents

Our prospective cohort study was approved by the ethics committee of Bern University Hospital and University of Bern (KEK No. 165/10, Basec PB_2017_00574) and complies with the Declaration of Helsinki. All adults, as well as all adolescents and their parents, gave their written, informed consent. The study was performed at the Departments of Pediatric Neurology and Neurology, Bern University Hospital, Switzerland. Patients were recruited by mail or in-person and examined during regular outpatient consultations or by appointment. Inclusion criteria were proven focal or generalized epilepsy (irrespective of medication intake) and age ≥ 14 years. Patients with early epileptic encephalopathy were excluded.

Data availability

Upon request.

Results

Data from the following two cohorts were utilized: (1) 20 adolescent and 21 adult patients with epilepsy recruited between 2015 and 2018, and (2) 63 adults from our previous studies (23 individuals from the study in reference [23] and forty individuals from the study in reference [24], eAppendix 1). Of the 104 patients tested, 95 met the data analysis criterion of stimulus appearance on average during the IEDs ($\bar{x}_{IED\ duration} - \bar{x}_{trigger\ latency} \geq 0$): 18 adolescents and 20 adults were recruited during 2015-2018, and 57 adults were recruited from previous studies.[23,24] These patients completed 155 test sessions in total (eAppendix 1). Female-to-male ratio was 48:47; mean adolescent age was 15.7 yrs. (min. 14, max. 17) and mean adult age was 37.8 yrs. (min. 18, max. 76). Codified patient information included epilepsy type/syndrome, antiseizure medication (including dose), patient age at testing, and sex (eTable 1). Patients had idiopathic generalized epilepsies, epilepsies of unknown origin, non-acquired focal epilepsies, or structural epilepsies.

RT and miss/crash are affected by IEDs and vary with IED type and IED duration

IEDs increased median RT by 75.3 ms ($p < 0.01$, Wilcoxon test), but median miss/crash probability remained at zero (table 1). Session miss/crash probabilities between normal EEG and IED nevertheless differed ($p < 0.01$, Wilcoxon test) because there were sessions with miss/crash during normal EEG and during IED, but their miss/crash probabilities were too few to be reflected in the median. Single IED-bursts increased miss/crash probability from 0.1% during normal EEG to 4.6% ($p < 0.01$, Chi-square test; table 1).

Median session RT-prolongation increased from focal IED (48 ms, 10-90%-IPR 100.0 ms), to generalized atypical IED (77.0 ms, 10-90%-IPR 160.9 ms), and generalized typical IED (164.0 ms, 10-90%-IPR 498.0 ms) ($p < 0.01$ Kruskal-Wallis test; figure 2B). Median session miss/crash probability$_{IED}$ was zero for focal IED (0%, 10-90%-IPR 5.6%) and generalized atypical IED (0%, 10-90%-IPR 8.9%), and increased to 14.7% (10-90%-IPR 38.6%) in generalized typical IED ($p < 0.01$ Kruskal-Wallis test; figure 2D). Single IED-burst miss/crash probability increased from focal IED (1.0%), to generalized atypical IED (2.5%), and generalized typical IED (22.4%) ($p < 0.01$ chi-square test; figure 2E).

On a session level, median duration of IEDs without miss/crash was comparable between focal and generalized atypical IEDs (1384.0 ms, 10-90%-IPR 1867.0 ms vs. 1359.0 ms, 10-90%-IPR 1324.6 ms), and were longer for generalized typical IEDs (2374.0 ms, 10-90%-IPR 4435.5 ms) ($p < 0.01$ generalized atypical vs. generalized typical IED, Kruskal-Wallis test; figure 2C). A similar pattern could be observed for median session duration of IEDs with miss/crash with the longest duration of generalized typical IEDs (3155.0 ms, 10-90%-IPR 9514.0 ms) ($p = 0.03$ for generalized atypical IED vs. generalized typical IED, Kruskal-Wallis test; figure 2F). No difference was found for median IED frequency per minute of test sessions according to IED type ($p = 0.22$, Kruskal-Wallis test; figure 2A). Left-hemispheric and right-hemispheric focal IED-bursts did not differ with respect to RT-prolongation (left:

32.7 ms, right: 56.8 ms; $p = 0.22$, Mann-Whitney test) and single IED-burst miss/crash

probability (left: 0.9%, right: 1.0%).

We performed a similar set of analyses when sessions were grouped according to test type.

Median IED-associated RT-prolongation was comparable between the flash test (56.4 ms, 10-90%-IPR 190.9 ms), car test (75.5 ms, 10-90%-IPR 146.1 ms), and simulator (86.6 ms, 10-90%-IPR 311.7 ms), indicating non-superior sensitivity to detect IED effects on this

behavioral measure ($p = 0.25$, Kruskal-Wallis test; figure 3B, table 1). Similarly, median

miss/crash probability$_{IED}$ was zero for each of the three tests, indicating non-superiority in

detecting IED-associated miss/crash when analyzed on a session level ($p = 0.29$, Kruskal-

Wallis test; figure 3D, table 1). Conversely, when the session level was resolved and data

were analyzed according to single IED-burst miss/crash probability, a difference emerged in

the percentage of miss/crash detected (car test 5.1% > flash test 4.8% > simulator 1.5%) ($p = 0.02$, chi-square test; figure 3E). The duration of IEDs without miss/crash was lowest in the

simulator (941.8 ms, 10-90%-IPR 700.1 ms) when compared to the flash test (1469.0 ms, 10-90%-IPR 1726.6 ms) and car test (1511.0 ms, 10-90%-IPR 1833.0 ms) ($p < 0.01$, Kruskal-

Wallis test; figure 3C). Duration of IEDs with miss/crash did not differ between the test types

($p = 0.38$, Kruskal-Wallis test; figure 3F). A clear difference in duration was found when

IEDs without miss/crash (1403.0 ms, 10-90%-IPR 1869.9ms) and IEDs with miss/crash

(2481.0 ms, 10-90%-IPR 4512.0ms) were contrasted at the session level ($p < 0.01$, Mann-

Whitney test; figure 4A). In a subgroup analysis, we examined all the above parameters

separately for adolescents and adults who were comparably affected by IEDs, in terms of both

session miss/crash probability and RT-prolongation, independent of the test used (table 1,

eAppendix 1).

Predictive power of IEDs for risk assessment of miss/crash

The empirical cumulative distribution function related the difference in cumulative miss/crash probability between IED and normal EEG to the RT-prolongation (figure 4B). The first inflection point was calculated to be 8.5% at a mean RT-prolongation of 62.1 ms. The difference in cumulative miss/crash probability between IED and normal EEG was calculated to be 50% at a mean RT-prolongation of 149.4 ms, and 20% at a mean RT-prolongation of 90.3 ms (figure 4B). Twenty-two percent of 155 sessions contained at least one IED-associated miss/crash. Fifty-six percent of sessions had a mean RT-prolongation of >62.1 ms and 16% of sessions had a mean RT-prolongation of >150.0 ms. The differences in miss/crash probability between IED and normal EEG as well as RT-prolongations were grouped by IED type, and the empirical cumulative distribution function was calculated for each subgroup (figure 4D). *From this, the relative difference in cumulative miss/crash probability was almost twice as high for generalized typical IEDs as for generalized atypical IEDs and about five times higher than for focal IEDs.*

The odds ratio of a miss/crash during IED was increased 4.9-fold (relative risk 2.7-fold) compared to normal EEG in our simulator (figure 4C, eTable 3 analysis 22). The rare case of miss/crash during normal EEG was most likely due to an attentional deficit ("daydreaming").

Influence of biological or environmental factors on driving performance and comparison with IEDs

In a computerized response speed test with RTs of 489 – 494 ms in rested and fasting patients, wakefulness of 18 hours prolonged RT by 45 ms, whereas a blood-alcohol concentration of 0.05% or 0.1% prolonged RTs by 45 ms and 77 ms, respectively.[26] In our car test, the median RT was 474 ms during normal EEG and was prolonged by a median 76 ms when all IEDs were combined.

More than 21 h of wakefulness or 0.08% blood-alcohol concentration caused a relative performance decline of 5-10% in a computer tracking task.[27] Standard doses of the sleeping aids, zolpidem or zopiclone, when taken 4.5 hours or 10.5 h before a car trip, increased standard deviation of lateral car position (on real road) by 3.4 cm (+18%) or 2.5 cm (+14%), respectively.[28] An increase in standard deviation of lateral car position by 2.4 cm could be caused by a blood-alcohol concentration of 0.05% and was considered a benchmark.[29] The IED-associated relative RT-prolongation was +18% (502.6 ms during IED /423.5 ms during normal EEG = 1.185) for all patients with epilepsy and all test types combined. Relative RT-prolongation ranged from +13% for focal IED-bursts to +38% for generalized typical IED.

The alcohol-related relative risk of driver involvement in fatal and non-fatal crashes as a function of blood-alcohol concentration was re-examined using recent real-road data.[30] The relative risk was approximated by the odds ratio. The relative driver involvement risk for non-fatal crashes was increased by a factor of 2.3-3.9 at a blood-alcohol concentration of 0.035% (2.3 for road users >20 yrs.; 3.9 for road users 16-20 yrs.), and with a blood-alcohol concentration of 0.065% it increased by a factor of 4.8-12.6 (4.8 for road users >20 yrs.; 12.6 for road users 16-20 yrs). In our study, the odds ratio to suffer a miss/crash in the simulator during IED was increased by a factor of 4.9 (95%-CI 1.5-16.1) compared with normal EEG. The higher odds ratio of 16- to 20-year-old road users could not be reproduced in our epilepsy patients with the simulator (data not shown). In a meta-analysis of 7000 participants with self-reported drowsiness in real-road driving, the pooled odds ratio of being involved in a traffic accident while driving drowsy was increased by a factor of 2.5 (95%-CI 1.9-3.4).[31]

Expected RT-prolongations and miss/crash probabilities for IEDs of a given type and duration

We calculated RT-prolongations and miss/crash probabilities for single IED-bursts (eMethods). We grouped these values according to IED type and sorted the RT-prolongations

and miss/crashes by the duration of their IEDs from minimum to maximum in each group. We created three duration-intervals: <1000ms, 1000-2000ms, >2000ms for focal IEDs, and <1000ms, 1000-3000ms, and >3000ms for generalized IEDs. We mapped the median RT-prolongations and miss/crash probabilities due to single IED-bursts for each IED type to these duration-intervals (table 2). We divided all 148 sessions that contained IEDs into two groups: 121 sessions that contained only IEDs without miss/crash, and 27 sessions that contained both IEDs with miss/crash and without. The rationale behind this division was that the two groups were expected to behave differently regarding RT-prolongation,[24] which they did not when the corresponding duration-intervals were compared (Mann-Whitney test not significant, data not shown). IED frequency in the 121 sessions (0.48/min, 95%-CI 0.38-0.64) was comparable to that in the 27 sessions (0.63, 95%-CI 0.39-0.86) ($p = 0.23$, Mann-Whitney test, data not shown). The situation was different for the duration of IEDs without miss/crash, which was shorter in the 121 sessions (1427 ms, 95%-CI 1398-1477) than in the 27 sessions (1904 ms, 95%-CI 1749-2052) ($p < 0.01$, Mann-Whitney test, data not shown).

Discussion

In this study, we identified IEDs that are clinically relevant to the fitness-to-drive of individuals with epilepsy as determined in three different test types.

Determinants of IED effects in fitness-to-drive evaluation and their variabilities

Our data confirmed that the IED type, that is focal or generalized distribution over the hemispheres, and configuration of epileptiform potentials (also called morphology in previous work,[14]) were important determinants for IED effects. Longer duration increased the probability for an IED-induced deficit.[14,32] Other determinants may include IED amplitude,[18,32] and increased EEG power during epileptiform discharges (called ramp-configuration of EEG spectrum,[33]).[18] IEDs were, however, variable within EEG recordings.

The subset of neurons involved in generating an IED in each patient varies from one spike to the next, that is, the neuronal ensembles that generate IEDs are probabilistic.[34,35] Diurnal fluctuation in IED number also contributes to variability.[36] The variability of IED *effects* (see, for example, standard deviation of RT-prolongations in eTable 1) can in part be explained by the coincidence of the probabilistic nature of IED generation with a probabilistic nature of information processing, that is neuronal information is also not represented by a specific spatiotemporal pattern of electrical activity.[34] Finally, the intra- and interindividual variability of IED effects may also be due to IED interaction with the test task. That is, tasks that engage a brain region with somatotopically arranged information processing, such as the primary visual cortex, may exhibit higher anatomical-functional specificity of IED effects than tasks that require networks for their processing, such as language, the prefrontal network for decision making, and probably the planning and execution of motor tasks.

Non-inferiority of simple tests compared to a realistic driving simulator

We expanded our reaction tests and added a driving simulator. The main reason was to improve the transferability of laboratory results to the real road.[37] We could have chosen lane deviation, and thus "standard deviation lateral position", as an indicator of IED effects, as in previous work.[38,39] However, we decided to use the total stopping distance as a more descriptive parameter than lane deviation, but unfortunately the use of total stopping distance failed due to the variation in the participants' driving speeds (eAppendix 1). Notably, session RT-prolongation and session miss/crash probability were not significantly influenced by the test used, suggesting that the effectiveness of a simple driving videogame or flash test is *non-inferior* to a realistic driving simulator in assessing IED-related miss/crash and RT-prolongation. We thus failed to show, that increased task difficulty, which is associated with the simulator in comparison to the flash test and car test, provided greater sensitivity for IED-induced deficits, as was suggested previously.[15] We confirmed for IEDs without miss/crash, that increased task difficulty reduced IED number and shortened IED duration,[14-16] using

simulator data in comparison to data from the flash test and car test. We did however note that duration of IEDs with miss/crash was comparable across the three different tests, probably due to a stronger epileptogenic field of miss/crash IEDs. The laterality of focal IEDs did not affect the IED-induced deficit in our three tests. We had recorded too few single focal IEDs to test bi-frontal location separately. In the only study that analyzed IED effects on real road, two of the three patients with the greatest increase in standard deviation of lateral car position had focal discharges involving the frontal lobe (fronto-temporal right and bi-frontal more on the left).[39] Future studies should focus on the location of focal IEDs rather than on their laterality to study the anatomical-functional specificity of IED-induced deficits in simulated driving.

A clinically relevant IED

A threshold of concern exists for epileptic seizures. A patient can drive if they have an annual seizure recurrence risk of up to 20%.[7,8] A threshold of concern for a clinically relevant IED has not yet been formulated. In our previous work,[24] we have theoretically proposed a clinically relevant IED as the 99th percentile of the standard deviation of the mean reaction time of young healthy volunteers and have set it to 100ms. We now propose a 20% miss/crash risk at a RT-prolongation of 90.3 ms as a clinically relevant IED effect, based on the cumulative distribution curve we have calculated for the two variables. The predictiveness of IED-associated RT-prolongation, which is usually measured much more frequently in a test than a missed reaction or crash, can be used to identify a clinically relevant IED. The essence of an IED with a missed reaction or crash is cognitive impairment, which is related to impaired awareness seizures that are known to cause the most accidents when they occur while driving.[3]

Translation of IED effects to the real road

We limited our research to the effects of drowsiness, medication intake, and alcohol while driving. The idea of using blood-alcohol related impairment as a comparator across studies was proposed by others,[26,27] and is based on the substantial contribution of drinking and driving to real-road traffic accidents and the large number of studies on the subject. The IED-associated odds ratio and relative risk for a missed reaction in our simulator is comparable to an estimated odds ratio for a crash by self-reported drowsiness while driving,[31] and to an estimated relative risk for collisions in the driving simulator from a blood-alcohol concentration between 0.05%-0.1% (eAppendix 1),[40] and to an odds ratio for a non-fatal crash on real roads from a blood-alcohol concentration around 0.035%.[30] It is important to carefully consider this translation of IED effects to the real road and identify the clinically relevant IEDs either by measuring their effect (see previous paragraph) or by analyzing the electrophysiological features of IEDs in a routine EEG (next paragraph).

Decision aid with expected IED effects in a routine EEG

Our decision aid (in table 2 and with practical examples in eAppendix 1) assists in determining who is eligible for a fitness-to-drive test, by providing the EEG reader with the expected transitory deficits for IEDs of a given type and duration. We recommend testing if EEGs show predominantly focal IED-bursts with greater than 2 second duration or generalized IEDs with greater than 3 seconds duration. When EEGs contain generalized IEDs of 1000-3000 ms duration, it is recommended that the testing depends on the IED frequency per session (above 0.5/min) and the patient's contextual factors. From a clinical perspective, the IEDs that form the basis for assigning patients to behavioral testing are also the IEDs that we would classify as clinically relevant if there were no options for fitness-to-drive testing. The aim is not to test as many patients as possible but to individualize decisions about the fitness-to-drive, and to standardize the decisions with respect to practices at different epilepsy clinics.

Study limitations

Long trigger latencies, even with automated IED detection in the simulator, did not allow us to measure the effects of solitary epileptiform spikes. We are currently working on a real-time IED detection and stimulus triggering algorithm. In classical literature and more recent work,[14,15,39,41-44] the definition of an IED was variable, but so were the purposes of the studies. We believe that the search for the best possible IED criteria to study their effects on daily social functioning of the awake epilepsy patient is a work in progress.

Conclusion and outlook

IEDs have recently become increasingly important in research focused on impaired consciousness,[e.g.,11,18-19] dementia,[45-47] and seizure prediction,[36] but are also a phenomenon with everyday social consequences. We have created a decision aid for fitness-to-drive evaluation and propose a clinically relevant IED effect. A flash test or a (freely available) car test can be used to screen for IED-induced deficits in regular clinical practice (for example, in 20 minutes). Future longitudinal studies should focus on determining which IEDs are treatable, and if so, whether the IEDs relevant to regaining fitness-to-drive can be suppressed, and if the therapeutic goals can be achieved to improve the patient's quality of life. New machine learning approaches and automated neuropsychological bedside tests can assist in improved testing of IED-induced deficits.

Appendix 1

Name	Location	Contribution
Heinz E. Krestel, MD	Yale University, USA, University Hospital Frankfurt, DE	Designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; acquired funding; had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis
David Schreier, MD	Bern University Hospital and University of Bern, CH	Major role in the acquisition of data
Elmaze Sakiri, MD	Bern University Hospital and University of Bern, CH	Major role in the acquisition of data
Andreas von Allmen, MSc	Yale University, USA	Devised patent and built custom-made devices for this study; revised the manuscript for intellectual content
Yasmina Abukhadra	Yale University, USA	Interpreted the results, analyzed the data; revised the manuscript for intellectual content
Arto Nirkko, MD	Neurocenter Lucerne, Lucerne, CH	Interpreted the results; revised the manuscript for intellectual content
Maja Steinlin, MD	Bern University Hospital and University of Bern, CH	Interpreted the results; revised the manuscript for intellectual content

Felix Rosenow, MD	Epilepsy Center Frankfurt Rhine-Main, Frankfurt, DE	Interpreted the results; revised the manuscript for intellectual content
Rune Markhus, MD	National Centre for Epilepsy, Oslo, NO	Interpreted the results; revised the manuscript for intellectual content
Gaby Schneider, PhD	Institute of Mathematics, Goethe University, Frankfurt, DE	Analyzed the data and interpreted the results; revised the manuscript for intellectual content
Caroline Jagella, MD	Yale University, USA	Analyzed the data and interpreted the results; revised the manuscript for intellectual content
Johannes Mathis, MD	Bern University Hospital and University of Bern, CH	Interpreted the results; revised the manuscript for intellectual content
Hal Blumenfeld, MD, PhD	Yale University, USA	Designed and conceptualized the study, analyzed and interpreted the results, revised the manuscript for intellectual content

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Figure legend

Figure 1. Reaction tests.
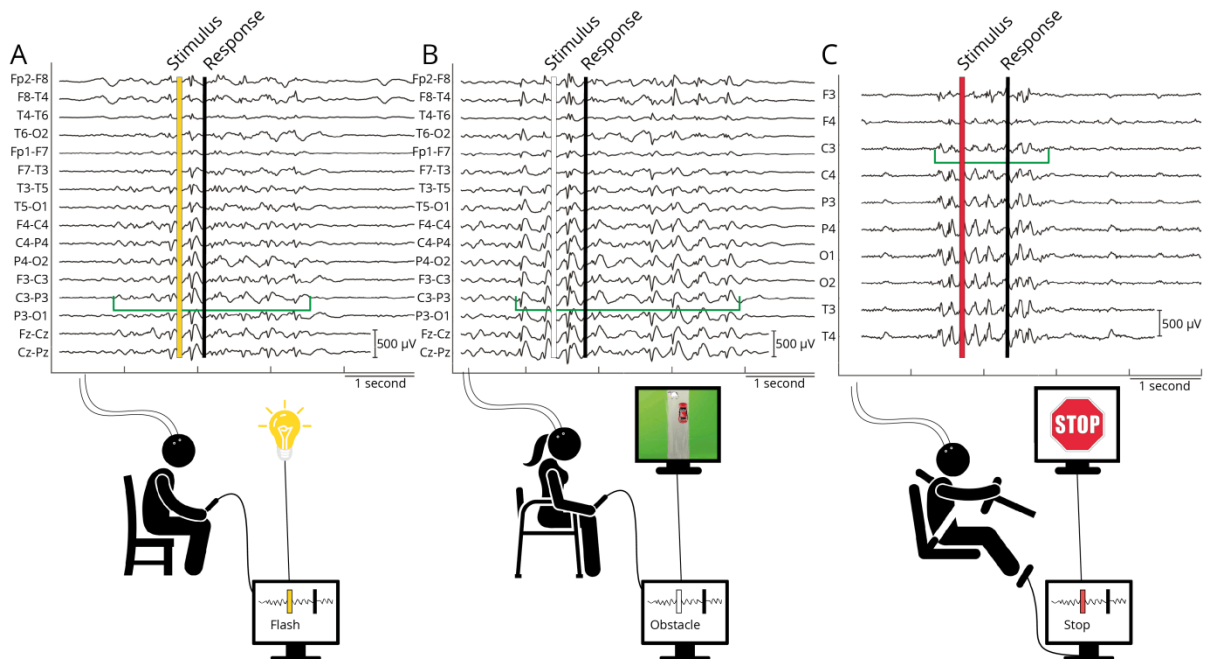
A) Patients with closed eyes reacted to a single light flash by button-press while scalp EEG was recorded. Single flashes from a flickering light were manually triggered as soon as each IED was recognized. A yellow vertical bar indicates single flash appearance, IED onset and end are marked with vertical green lines, and duration is indicated by a horizontal green line. The trigger latency is the difference in time between the green horizontal bar indicating the onset of the IED and the yellow vertical bar indicating the appearance of the visual stimulus triggered by the experimentalist. Single flashes were triggered in random fashion during normal EEG (not shown). **B)** Patients played a car driving video game (car test) on a laptop. An obstacle (whitish cow on gray road, shown on the small monitor) appeared in the lane of a red car and the patient had to change lanes by pressing a button, otherwise the car crashed into the obstacle. Obstacles were triggered manually when an IED was detected and randomly during normal EEG. **C)** Patients drove in a realistic driving simulator with an "empty highway at night" scenario projected in front of the driver. Red stop signs were triggered manually at random during normal EEG, and by a real-time detection algorithm during IEDs. Patients responded by right-foot brake.

Figure 2. RT-prolongation and miss/crash vary with IED type and IED duration.
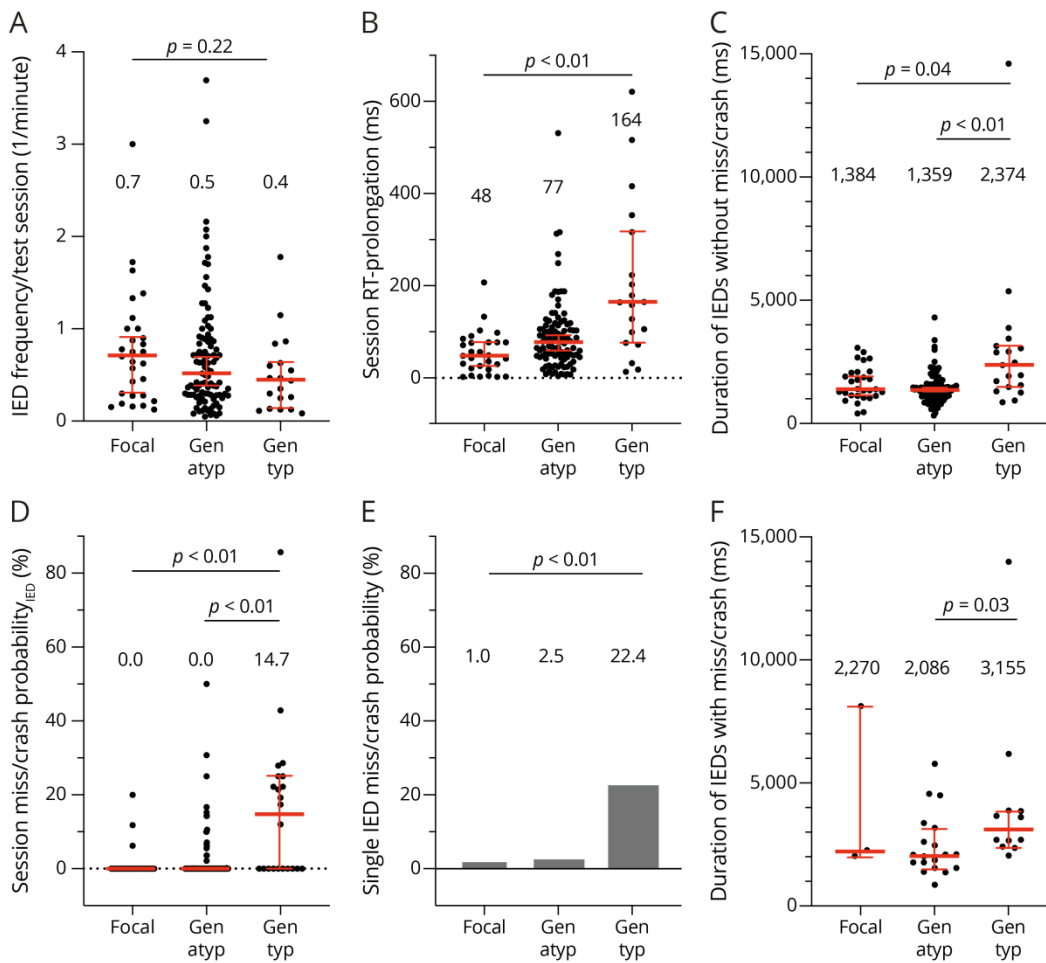

A) The number of IEDs from test sessions classified as having predominant focal, generalized atypical (gen atyp), or generalized typical (gen typ) IEDs was divided by the respective duration of the test session in minutes to get a metric of IED frequency. Each point of the scatter plot corresponds to the IED frequency of a session. The metric was presented as median with 95% confidence interval (95%-CI) in red (medians written above scatter plots). **B)** IEDs without miss/crash generally resulted in RT-prolongation. RT-prolongation of each session (represented as one point) was grouped according to the IED type of the session. The appropriately grouped RT-prolongations were presented as median with 95%-CI. **C)** The average duration of IEDs without miss/crash of each session (represented as one point) was

grouped according to the IED type of the session. The median with 95%-CI is shown for each group of IED durations. **D)** At the session level, IED-associated missed reactions in the flash test and simulator, and IED-associated crashes in the car test were divided by the total number of stimulus exposures during IED (each point corresponds to the miss/crash probability$_{IED}$ of a session). Miss/crash probabilites$_{IED}$ were grouped by IED type and presented as median with 95%-CI. **E)** To calculate the single IED-burst miss/crash probability separately for each IED type, the session level was resolved. Of all sessions classified as focal, generalized atypical, or generalized typical, the respective total number of IEDs with misses/crashes was divided by the respective total number of stimulus exposures during each IED. This plot is intended to complement the session miss/crash probability$_{IED}$ in (D) to show that miss/crash did occur in sessions that were classified as focal or generalized atypical. **F)** The session average of IED duration for IEDs with miss/crash (shown as one point) was grouped according to the IED type of the session. The descriptive statistics used was the median with 95%-CI (in red).

Figure 3. RT-prolongation and miss/crash on a session level are not influenced by test type.
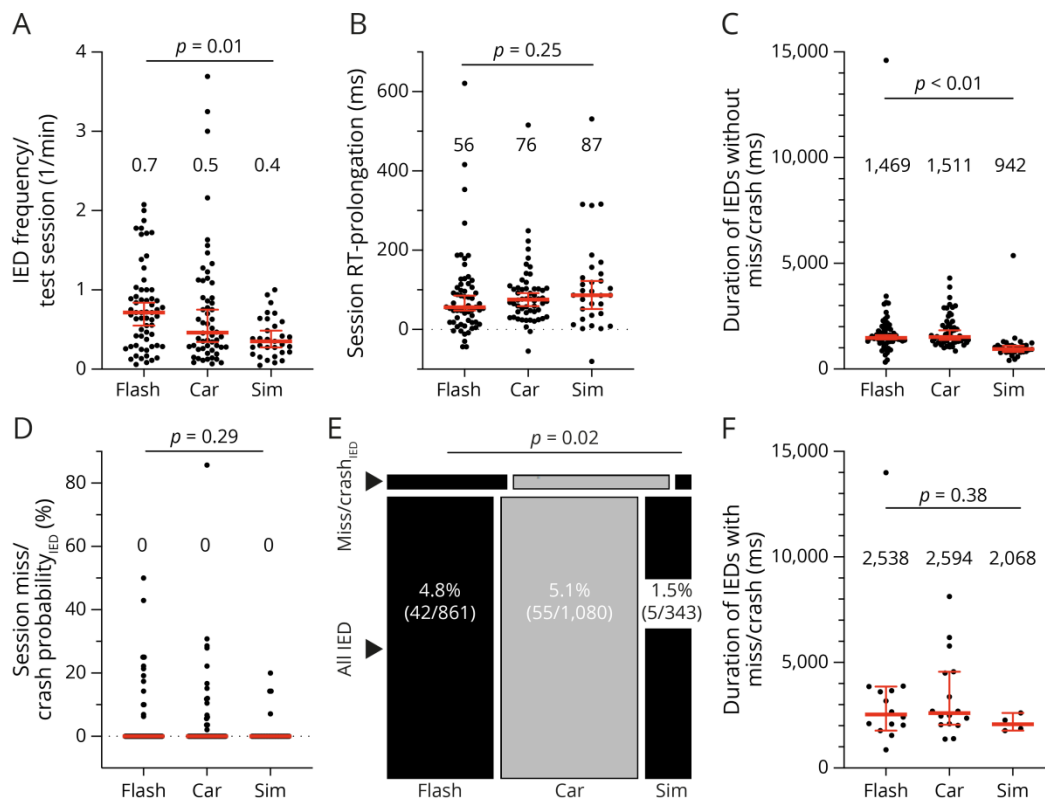

A) The session IED frequency was calculated as the number of IEDs divided by the duration of the test session in minutes and grouped according to session test type (flash test, car test, simulator). Each point of the scatter plot corresponds to the IED frequency of a session. The descriptive statistics used for session IED frequencies was the median with 95%-CI (in red, medians written about scatter plots). **B)** Session RT-prolongation (shown as one point) was grouped by test type. The correspondingly grouped session RT-prolongations were described with the median and 95%-CI. **C)** The average duration of IEDs without miss/crash of each session (equivalent to one point) was grouped by test type. The median with 95%-CI is shown for each group of IED durations. **D)** Session miss/crash probability$_{IED}$ was grouped by test

type and described using the median and 95%-CI. **E)** Single IED-burst miss/crash probability

is shown as a mosaic plot, grouped by test type, and generated from a contingency table. The

areas of the rectangles reflect the ratio between the total number of IEDs with misses/crashes

(miss/crash$_{IED}$) and the total number of stimulus exposures during the IED (all IED) of each

test type. For example, for the flash test, 42 divided by 861 gives 4.8%. The areas of the

rectangles are in the (graphically vertical) ratio of 0.048 (miss/crash$_{IED}$) to 1 (all IED) for the

flash test. But they are also in the (graphically horizontal) ratio between the test types

according to the calculated percentages to each other. **F)** The average duration of IEDs with

miss/crash of each session (equivalent to one point) was grouped by test type. The median

with 95%-CI is shown for each group of IED durations.

Figure 4. Predictive power of IEDs for risk assessment of miss/crash.
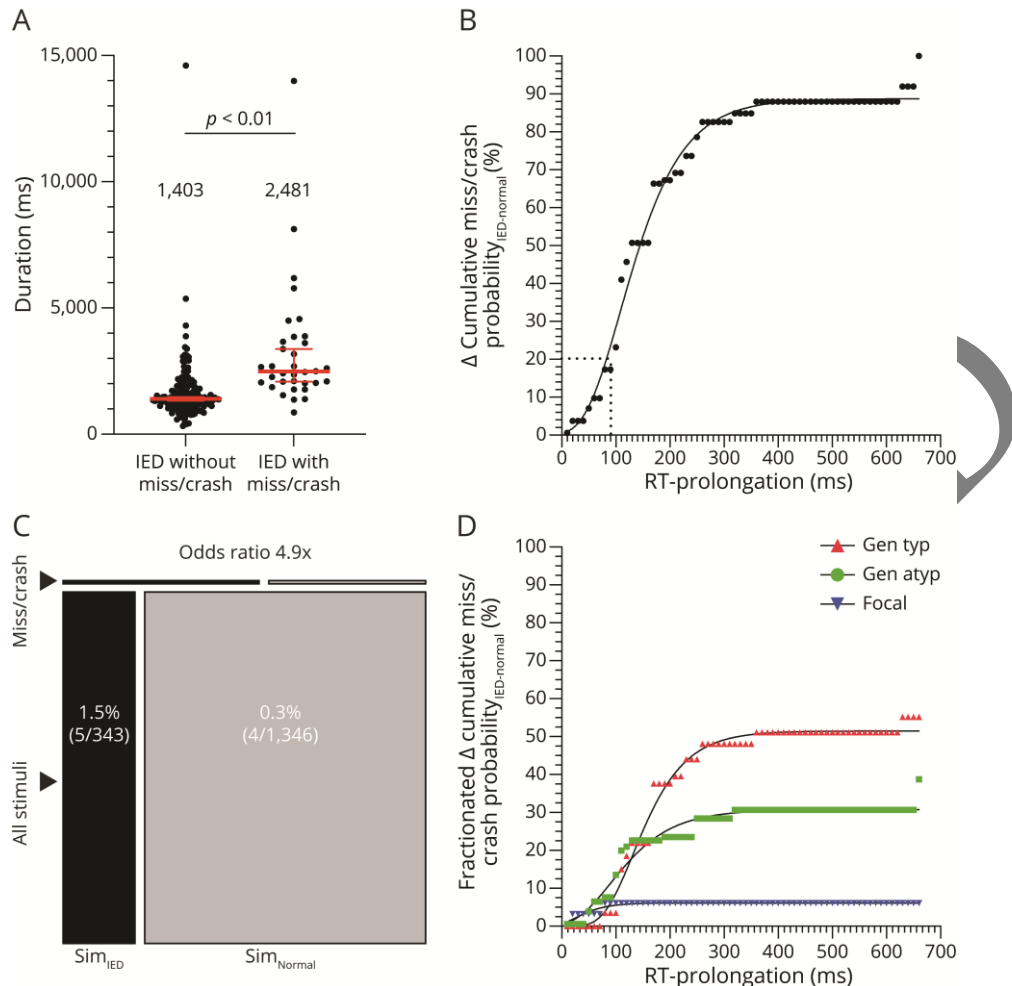
A) The average duration of IEDs without miss/crash from 121 sessions plus the average

duration of IEDs without miss/crash from 27 sessions that included both IEDs without

miss/crash and IEDs with miss/crash is shown in this scatter plot above the label "IED

without miss/crash" (one dot represents one session). The average duration of IEDs with

miss/crash from each session with at least one miss/crash (from 27 sessions that included both

types of IEDs and from 7 sessions that included only IEDs with miss/crash) was included in

the "IED with miss/crash" category. Grouped session data were described with the median

and 95%-CI (in red, medians written above scatter plots). **B)** Empirical cumulative

distribution function showing the accumulated difference in miss/crash probability between IED and normal EEG as a function of RT-prolongation. 20% of misses/crashes (horizontal dotted line) were associated with RT-prolongations ranging from 1 ms to X = 90.3 ms (vertical dotted line). **C)** The single IED-burst miss/crash probability in the simulator (Sim_{IED}) was 1.5% (visualized as the proportion of the thin black rectangle labeled "miss/crash," relative to the larger black rectangle below labeled "all stimuli"). The probability of suffering a miss/crash from a single visual stimulus during normal EEG in the simulator (Sim_{Normal}) was 0.3% (visualized as the proportion of the two gray rectangles). The odds ratio of experiencing a miss/crash during an IED was increased 4.9-fold compared to experiencing a miss/crash during periods of normal EEG (the proportion of the black rectangles compared to that of the gray rectangles). The respective numerical ratios were visualized as corresponding area ratios in a mosaic plot for the simulator. **D)** The differences in miss/crash probability between IED and normal EEG as well as RT-prolongations were grouped by IED type, and the empirical cumulative distribution function was calculated for each subgroup. Compared with the curve in (B), it shows the relative accumulated difference in miss/crash probability between IED and normal EEG as a function of RT-prolongation, grouped by sessions with predominantly generalized typical IED, generalized atypical IED, and focal IED.

Table 1. Select key results of RTs and misses/crashes for all patients and all test types, grouped according to test type, IED type, and age groups.

The mean values of the RTs acquired during normal EEG (Normal) and during IEDs for each session, and their differences (RT-prolongations, ΔRT), were grouped according to the experimental conditions. The grouped data are expressed as medians (10-90% interpercentile range, IPR). Similarly, the session miss/crash probabilities were grouped in the same way and the data are presented as medians (10-90%-IPR). Missed reactions or crashes are given as single IED-burst probability (single miss/crash) when sessions were resolved and all individual data were pooled. The number of sessions used for calculation is given in the first column of each experimental condition. In the top row, RT and both single IED-burst miss/crash probability and session miss/crash probability are given for all patients and all tests. In the second row from the top, the RTs from the first row were grouped by test type and nested by IED class for each test type. The third row shows the miss/crash probability, grouped by test type and nested by IED class for each test type. The fourth and fifth rows show the RTs and miss/crash probabilities for the adolescent cohort grouped by test type. The last two rows show the RTs and miss/crash probabilities for the adult cohort grouped by test type.

Table 2. Expected RT-prolongations and miss/crash probabilities for IEDs of a given type and duration. This table guides the EEG reader through the RT-prolongations or miss/crash probabilities that can be expected when a routine 10/20 surface EEG is recorded and IEDs are detected therein. We have created three clinically practicable duration-intervals: <1000ms, 1000-2000ms, >2000ms for focal IEDs, and <1000ms, 1000-3000ms, and >3000ms for generalized IEDs. We mapped the RT-prolongations and miss/crash probabilities due to single IED-bursts for each IED type to these duration-intervals (ΔRT and miss/crash). The number of RT-prolongations used to calculate the median, expected RT-prolongations is reported as the IED measures in each duration-interval. Similarly, the number of IEDs used to calculate the expected miss/crash probability is reported as No. of IED in each duration-interval. We divided 148 sessions into 121 sessions that contained only IEDs without miss/crash (top row), and 27 sessions that contained both IEDs with miss/crash and without (middle row). For these 27 sessions, RT-prolongations are given only for the IEDs without miss/crash. Data from all 155 sessions of this study were included for the calculation of single IED-burst miss/crash probability (bottom row). RT-prolongations due to single IED-bursts are described as median (10-90% interpercentile range, IPR). Single IED-burst miss/crash probability is expressed as [%] (for comparison, the miss/crash probability for periods during normal EEG is about 0.1%, table 1).

RT, all patients, all test types, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
148	423.5 (370.9)	502.6 (495.1)	75.3 (181.6)

Single miss/crash, all patients, all test types, [%]

Sessions	Normal	IED	p value (x^2)
155	0.11 (8/7602)	4.6 (102/2207)	< 0.01

Session miss/crash probability, median [%] (IPR)

Sessions	Normal	IED	p value (Wilcoxon)
155	0.0 (0.0)	0.0 (17.0)	< 0.01

RT, all patients, flash test (eyes closed), median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
61	315.2 (190.1)	381.3 (287.5)	56.4 (190.9)
Focal IED	309.7 (253.5)	379.3 (304.4)	33.8 (167.5)
Gen. atyp. IED	313.5 (172.2)	380.6 (251.6)	54.5 (175.8)
Gen. typ. IED	352.4 (161.7)	531.3 (558.3)	164.0 (608.3)

RT, all patients, car test (eyes open), median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
56	473.5 (222.7)	527.6 (306.7)	75.5 (146.1)
Focal IED	476.1 (210.8)	524.0 (227.6)	71.2 (93.0)
Gen. atyp. IED	446.6 (198.4)	497.6 (199.2)	68.5 (117.1)
Gen. typ. IED	522.6 (363.0)	683.6 (671.0)	161.4 (484.1)

RT, all patients, simulator (eyes open), median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
31	627.6 (483.3)	689.5 (619.1)	86.6 (311.7)
Focal IED	597.4 (209.5)	642.0 (256.2)	30.8 (205.3)
Gen. atyp. IED	669.2 (538.7)	765.5 (695.9)	103.4 (306.1)
Gen. typ. IED (n=2)	551.8 (92.6)	747.8 (147.4)	196.0 (240.1)

Miss/crash, all patients, flash test, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
67	0 (0/2037)	5.2 (42/804)	0.0 (21.6)
Focal IED	0 (0/341)	0.9 (1/114)	0.0 (5.0)
Gen. atyp. IED	0 (0/1434)	2.2 (12/555)	0.0 (10.0)
Gen. typ. IED	0 (0/262)	21.5 (29/135)	19.2 (39.3)

Miss/crash, all patients, car test, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
57	0.1 (4/4219)	5.2 (55/1060)	0.0 (17.8)
Focal IED	0 (0/827)	0.8 (2/242)	0.0 (7.1)
Gen. atyp. IED	0.03 (1/2929)	3.1 (22/710)	0.0 (12.4)
Gen. typ. IED	0.7 (3/463)	28.7 (31/108)	12.0 (85.7)

Miss/crash, all patients, simulator [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
31	0.3 (4/1346)	1.5 (5/343)	0.0 (12.9)
Focal IED	0 (/221)	2.9 (1/34)	0.0 (20.0)
Gen. atyp. IED	0.4 (4/1004)	1.4 (4/284)	0.0 (11.4)
Gen. typ. IED	0 (0/121)	0 (0/25)	0.0 (0.0)

RT, Adolescents, flash test, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
10	336.2 (451.2)	400.4 (543.6)	74.0 (167.2)

RT, Adolescents, car test, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
7	404.5 (180.5)	524.0 (177.4)	102.2 (137.2)

RT, Adolescents simulator, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
12	655.4 (583.5)	811.8 (653.9)	135.5 (246.6)

Miss/crash, Adolescents, flash test, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
12	0 (0/566)	4.6 (7/151)	0.0 (39.3)

Miss/crash, Adolescents, car test, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
7	0 (0/615)	2.3 (2/88)	0.0 (16.7)

Miss/crash, Adolescents, simulator, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
12	0.7 (4/543)	1.8 (3/164)	0.0 (14.3)

RT, Adults, flash test, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
51	313.8 (176.0)	379.9 (290.3)	55.5 (195.4)

RT, Adults, car test, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
49	475.3 (230.0)	531.2. (346.6)	72.4 (156.6)

RT, Adults, simulator, median [ms] (IPR)

Sessions	Normal	IED	ΔRT (IED-Norm)
19	589.6 (428.8)	644.3 (640.9)	64.2 (313.9)

Miss/crash, Adults, flash test, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
55	0 (0/1471)	5.4 (35/653)	0.0 (21.8)

Miss/crash, Adults, car test [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
50	0.1 (4/3604)	5.5 (53/972)	0.0 (21.5)

Miss/crash, Adults, simulator, [%]

Sessions	Normal (Single miss/crash)	IED (Single miss/crash)	Session miss/crash_IED median (IPR)
19	0 (0/803)	1.1 (2/179)	0.0 (7.1)

table 1

Analysis of single IED-bursts without miss/crash in 121 sessions not containing any IED with miss/crash, all test types

RT-prolongation, median [ms] (IPR), mapped by IED type and duration-interval

Focal IED	IED duration [ms]			Gen. atyp. IED	IED duration [ms]			Gen. typ. IED	IED duration [ms]		
	< 1000	1000-2000	>2000		< 1000	1000-3000	> 3000		< 1000	1000-3000	> 3000
IED measures	63	163	148	IED measures	286	763	111	IED measures	24	48	3
ΔRT [ms]	3.3 (148.1)	32.1 (240.3)	63.4 (273.5)	ΔRT [ms]	50.2 (273.1)	49.6 (301.4)	25.5 (311.0)	ΔRT [ms]	50.9 (128.1)	78.5 (561.4)	124.5 (943.5)

Subgroup analysis of single IED-bursts without miss/crash contained in 27 sessions with ≥ 1 IED with miss/crash, all test types

RT-prolongation, median [ms] (IPR), mapped by IED type and duration-interval

Focal IED	IED duration [ms]			Gen. atyp. IED	IED duration [ms]			Gen. typ. IED	IED duration [ms]		
	< 1000	1000-2000	>2000		< 1000	1000-3000	> 3000		< 1000	1000-3000	> 3000
IED measures	4	7	8	IED measures	58	238	47	IED measures	4	70	60
ΔRT [ms]	11.4 (63.0)	62.5 (216.0)	66.5 (184.0)	ΔRT [ms]	85.9 (590.6)	63.2 (441.2)	65.6 (344.7)	ΔRT [ms]	7.3 (191.7)	137.3 (371.8)	152.1 (911.5)

Analysis of single IED-bursts with miss/crash, all patients and test types (155 sessions)

Missed reactions and crashes out of the number of single IED-bursts in [%], mapped by IED type and duration-interval

Focal IED	IED duration [ms]			Gen. atyp. IED	IED duration [ms]			Gen. typ. IED	IED duration [ms]		
	< 1000	1000-2000	>2000		< 1000	1000-3000	> 3000		< 1000	1000-3000	> 3000
No. of IED	67	170	160	No. of IED	345	1023	173	No. of IED	28	155	86
miss/crash [%]	0 (0/67)	0 (0/170)	2.5 (4/160)	miss/crash [%]	0.3 (1/345)	2.2 (22/1023)	8.7 (15/173)	miss/crash [%]	0 (0/28)	23.9 (37/155)	27.7 (23/86)

table 2

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