Supplementary material

Results

Sessions completed

Age group	Test type	Epi11	Epi16	Recruitment 2015-2018	Subtotal
Adolescents	Flash test			12	12
	Car test			7	7
	Driving simulator			12	12
	Subtotal			31	31
Adults	Flash test	20	31	4	55
	Car test	8	40	2	50
	Driving simulator			19	19
	Subtotal	28	71	25	124
Total		28	71	56	155

Of the adolescent persons with epilepsy, 1 completed all three tests, 11 completed two tests, and 6 completed only one test (together 31 sessions). Of the adults recruited between 2015-2018, 1 completed three tests, 3 completed two tests, and 16 completed only one test (together 25 sessions). Of the adults de-identified as Epi11,[23] 7 completed two tests, and 14 completed only one test (together 28 sessions). Of the adults de-identified as Epi16,[24] 28 completed both the car and flash test, and 15 completed only one test (together 71 sessions).

Of the 155 sessions recorded in total, 148 sessions fulfilled the criterion for IEDs without miss/crash to include on average a trigger ($\bar{x}_{IED\ duration} - \bar{x}_{trigger\ latency} \geq 0$). Thus, the respective $RT_{normal\ EEG}$, RT_{IED}, trigger latencies and IED durations of these one hundred forty-eight sessions were included in the study dataset. For 7 of the 155 sessions (flash A11, flash A12, flash Epi11_11, flash Epi11_24, flash Epi11_6c, flash Epi11_6d, and car Epi11_5b),

$\bar{x}_{IED\ duration} - \bar{x}_{trigger\ latency} \geq 0$ was only fulfilled for IEDs with miss/crash but not for IEDs without miss/crash. Thus, the miss/crash probability$_{ED}$, miss/crash probability$_{normal\ EEG}$, and the respective trigger latencies and durations of these IEDs with miss/crash were included, but all the data regarding IEDs without miss/crash were excluded. In total, 34 sessions had at least 1 miss/crash, and all fulfilled the criterion for IEDs with miss/crash to include on average a trigger ($\bar{x}_{IED\ duration} - \bar{x}_{trigger\ latency} \geq 0$).

Additional features of IEDs

We acquired the peak frequency of each IED in a test session in [Hz] by dragging a rectangle on the computer monitor over each IED of a session with the cursor and calculating a fast Fourier transform over each IED using the built-in function of NicOne software. The peak frequency of each IED was taken out of the power spectrum, averaged for all IEDs of a test session, and given as mean with standard deviation (SD) in eTable 1. We first asked whether peak IED frequency differed when sessions were grouped according to IED type. As expected, peak frequency was lowest in sessions with generalized typical IEDs with a median 3.7 Hz (10-90%-IPR 1.2 Hz), higher in sessions with generalized atypical IEDs (5.3 Hz, 10-90%-IPR 3.4 Hz), and highest in sessions with focal IEDs (5.7 Hz, 10-90%-IPR 4.7 Hz) ($p <$ 0.01, Kruskal-Wallis test; eTable 3 analysis 71). Unsurprisingly, peak IED frequency did not differ when sessions were grouped according to test type: flash test 5.0 Hz (10-90%-IPR 3.6 Hz), car test 5.0 Hz (10-90%-IPR 3.3 Hz), and simulator 5.5 Hz (10-90%-IPR 2.8 Hz) ($p =$ 0.14, Kruskal-Wallis test, eTable 3 analysis 72). Mean peak IED frequency did not linearly increase with RT-prolongation ($R^2 = 0.003$; eTable 3 analysis 73). We thus failed to show that a shift in the dominant frequency of the EEG power spectrum was related with IED-induced deficits. In previous work, a ramp configuration in power spectra (shift to higher frequency components but with decreasing power the higher the frequency component was) had been observed with spike activity in scalp EEG of patients with impaired awareness seizures

(psychomotor seizures). This ramp configuration in EEG power spectra was also observed in the same study during longer or missing responses compared to short responses in an auditory recognition task.[33] In another work, EEG power, calculated in W/Hz, was increased during seizures leading to impaired behavior in the continuous performance task or the repetitive tapping task when compared to seizures without impairment in these tasks.[18] In future studies, IED power, calculated in [W/Hz], should be correlated with IED-induced deficits, instead of using peak IED frequency in [Hz], to analyze this relationship in more detail.

Subgroup analysis for gender in relation to the effects of focal IED-bursts

We could show that RT-prolongation (female: 71.8 ms, male: 78.2 ms; $p = 0.62$, Mann-Whitney test) and single IED-burst miss/crash probability (female: 4.8%, male: 4.4%; $p = 0.70$, Fisher exact test) did not differ between males and females.

Miss/crash and RT are affected by IEDs, calculated separately for adolescents and adults

In a subgroup analysis, we examined RTs during normal EEG and IED, together with RT-prolongation, session miss/crash probability, single IED miss/crash probability, IED frequency per minute of test session, and IED duration separately for adolescents and adults (table 1, eTable 2). Beginning with adolescents, median RT-prolongations measured separately with each test differed with increasing values from the flash test (74.0 ms, 10-90%-IPR 167.2 ms) to the car test (102.2 ms, 10-90%-IPR 137 ms) to the simulator (135.5 ms, 10-90%-IPR 246 ms; $p = 0.02$, Kruskal Wallis test, table 1). A subgroup analysis of median RT-prolongations for each test by IED type showed a trend toward greater RT-prolongations during generalized typical IED only in the car test (eTable 2). The median session miss/crash probability$_{IED}$ was at zero for each test type, however with different 10-90%-IPRs (39.3 ms for the flash test, 16.7 ms for the. car test, 14.3 ms for the simulator; $p = 0.83$, Kruskal-Wallis

test; table 1, eTable 3 analysis 46). Statistical calculation of nested analysis by IED type, separately for each test, was omitted (eTable 2).

In adults, median RT-prolongations were comparable between the three tests (55.5 ms for the flash test, 72.4ms for the car test, and 64.2ms for the simulator; $p = 0.43$, Kruskal-Wallis test; table 1, eTable 3 analysis 45). The tendency for greater median RT-prolongation during generalized typical IED compared to generalized atypical and focal IED was evident in adults in the nested analysis by IED type in each of the three tests (eTable 2, rows 40-42, columns D, Q, AE). The median session miss/crash probability$_{IED}$ was at zero for each test type but again the 10-90%-IPR differed (flash test 21.8 ms, car test 21.5 ms, simulator 7.1 ms; $p = 0.30$, Kruskal-Wallis test; eTable 3 analysis 47). A nested analysis by IED type revealed a significantly higher session miss/crash probability for the flash test and the car test during generalized typical IED, when compared to the miss/crash probabilities of the flash test and car teset during focal or generalized atypical IED (eTable 2, rows 90-92, columns E, S (but not simulator in column AF)).

Total stopping distance, reaction distance, and braking distance in the simulator

Panel A of eFigure 2 shows all individual measurements for speed and total stopping distance (given as the median, 95%-CI). The measured speed during IED (71.6 km/h, 95%-CI 66.7-76.6) was slower than that during normal EEG (85.5 km/h, 95%-CI (83.1-88.5), $p < 0.01$, Mann-Whitney test; eFigure 2A), for which there were several reasons, including (1) a violation of the requirement to maintain a constant speed and (2) occasionally successive IEDs that prevented the target speed of 100 km/h (62.1 mph) from being reached (despite a refractory trigger period of 10 s) before braking again. Because the initial speed at the time of braking is highly relevant to the total stopping distance, different speeds resulted in overall shorter total stopping distance during IED (44.4 m, 95%-CI 38.7-49.0) compared to normal

EEG (55.0 m, 95%-CI 52.1-58.0; $p < 0.01$, Mann-Whitney test; eFigure 2A) (see the linear regression for the difference in total stopping distance between normal EEG and IED (Δ Stopp dist) and the difference in speed at the time of braking for normal EEG and IED (Δ Speed), $R^2 = 0.95$; eTable 3 analysis 57). To measure the effect of the IEDs, all factors in the equation for calculating the total stopping distance, that is, the initial and terminal speed, brake pressure buildup time, and brake deceleration had to be replaced by constants, except for the measured RT (see eMethods p.6). Total stopping distance at a set speed of 100 km/h at the time of braking as a function of measured RT during normal EEG was 71 m (95%-CI 70.7-71.2) and 73 m (95%-CI 72.3-74.1) during IED ($p < 0.01$, Mann-Whitney test; eFigure 2A). To illustrate the impact of IED on the total stopping distance, it is first necessary to explain that the total stopping distance is composed of the reaction distance and the braking distance. The reaction distance is the human factor, and the braking distance is based on the vehicle factors (such as braking pressure build-up time and braking deceleration due to tire contact with the road). The vehicle factors are constant in our application of the equation to calculate the total stopping distance. Thus, the IED effects are related to the reaction distance, a human factor. Panels B through E of eFigure 2 show the measured braking distance, measured and calculated reaction distances, and measured speed as bivariate data during normal EEG and during IED on a session level separately for adolescents and adults (median, 95%-CI). The measured reaction distance was obtained by multiplication of measured speed with the measured RT that is the time between stop sign appearance and right-foot braking. By subtracting the measured reaction distance from the measured total stopping distance, the measured braking distance was obtained. Measured braking distances were shorter during IEDs as compared to that during normal EEGs, separately for adolescents (normal: 43.0 m, 95%-CI 31.9-54.5; IED: 33.2 m, 95%-CI 17. 3-49.9; eTable 3 analysis 61) and for adults (normal: 37.2 m, 95%-CI 35.4-44.9; IED: 36.8 m, 95%-CI 26.1-41.1; eTable 3 analysis 62). This was visualized in the graph by the fact that most data were below the line of identity

(eFigure 2B, eTable 3 analyses 61, 62). Measured reaction distances were shorter during IED compared to normal EEG for adolescents (normal: 15.1 m, 95-CI 11.7-20.9; IED: 14.5 m, 95%-CI 12. 1-20.9; $p = 0.70$, Wilcoxon test, eTable 3 analysis 63), but longer during IED compared to normal EEG for adults (normal: 13.8 m, 95%-CI 10.9-16.3; IED: 14.2 m, 95%-CI 10. 0-17.4; $p = 0.74$, Wilcoxon test, eTable 3 analysis 64). For the statistical investigation of the differences in the bivariate distributions of measured reaction distances during normal EEG and IED between adolescents and adults, we used a nonparametric permutation test. The Euclidian distance between bivariate means served as a test statistic ($p = 0.62$, eFigure 2C). The measured speed on a session level was slower during IED than during normal EEG for adolescents (normal: 85.9 km/h, 95%-CI 66.4-97.5; IED: 74.6 km/h, 95%-CI 45.5-92.2) and for adults (normal: 79.1 km/h, 95%-CI 75.7-88.3; IED: 73.8 km/h, 95%-CI 62.9-85.6) (eFigure 2D). The reasons for the different speeds under the two experimental conditions are given in the description of eFigure 2A on p. 4. The calculated reaction distance was obtained by setting the initial speed at the time of right-foot braking to 100 km/h and multiplying this constant with the measured RT. The calculated reaction distances during normal EEG and IED are presented separately for adolescents and adults at a session level and are shown in eFigure 2E. The values are 18.8 m (95%-CI 16.6-26.1) for normal EEG and 22.7 m (95%-CI 18.7-30.4) during IED for adolescents ($p < 0.01$, Wilcoxon test, eTable 3 analysis 67), and 16.5 m (95%-CI 13.2-18.8) during normal EEG and 17.8 m (95%-CI 14.4-22.8) during IED for adults ($p < 0.01$, Wilcoxon test, eTable 3 analysis 68). The calculated reaction distance on a session level did not differ between adolescents and adults ($p = 0.52$, permutation test, eFigure 2E; eTable 3 analysis 70). Now that we had disentangled total stopping distance into reaction distance and braking distance, the IED effects could be analyzed separately. On visual inspection, the data scatter for the measured braking distance in eFigure 2B appears to be similar to the scatter of measured speed in eFigure 2D, in that most of the data points were below the line of identity which indicates equal values on the x-axis and y-axis. The data

scatter in eFigure 2C (measured reaction distance) lies mainly on the identity line, although both the measured reaction distance and the measured braking distance were exposed to the measured speed. It appears as if IED effects were acting on the reaction distance and compensating for the slower speed during IED, so that the data points are mainly on the identity line. By additionally controlling for initial speed at stop sign presentation, the calculated reaction distance showed the net effects of IEDs, that is, the data points were mainly above the line of identity as shown in eFigure 2C. This results in a median 3.6 m in adolescents and a median of 1.8 m in adults, given the difference in calculated reaction distance between normal EEG and IED. An Australian government website illustrates graphically and by video,[55] what a 4 m increase in reaction distance means at an initial speed of 100 km/h. This could correspond to a total stopping distance at an initial speed of 110 km/h, since at this speed the reaction distance is 4 m longer. If IED-induced deficits can persist for several 100 ms after the visible end of an epileptiform EEG discharge (see also study in reference [25] on the lingering effects after the visible end of generalized IEDs), and thus the reaction distance could be even longer or could influence the braking distance, for example, by not depressing the brake pedal sufficiently, then the total stopping distance could be even longer. Indeed, we confirmed the observation that the error rate in the continuous performance test of Mirsky and van Buren's "trough of consciousness"[25] did not immediately normalize after the cessation of the generalized epileptiform discharge in surface EEG. Our RTs or missed reactions and crashes, which were associated to stimuli that appeared in the interval between IED ending and up to 800 ms after the IED ending, were still markedly elevated compared with RTs and miss/crash during normal EEG. These results are not shown and are perhaps the focus of another study, because our analyses were not as detailed as data analyses in which the visual stimulus appeared during an ongoing IED. The most obvious explanation for impaired brain information processing after the cessation of epileptiform discharge in surface EEG is, as stated previously,[34] that the reactive inhibition of the cortical

focus itself (for focal IEDs) - and possibly the reactive inhibition of the contralateral homotopic cortex, thalamus, and nuclei distant from the cortical focus that occurs after an IED - generally lasts for several hundred and occasionally up to thousand milliseconds.

The importance of the temporal match of the test task and IED

Due to space limitations in the main text all values of the respective section are given here. The median trigger latencies on a session level showed the human latency of the medical personnel in detecting IEDs and manually triggering a stimulus in the flash test (1257.0 ms, 95%-CI 112.0-1423.0) and car test (1217.0 ms, 95%-CI 1065.0-1325.0) for IEDs without miss/crash (eFigure 3A, eTable 3 analysis 26). For IEDs with miss/crash, the latency was 1205.0 ms (95%-CI 1017.0-1785.0, flash test) and 1607.0 ms (95%-CI 1091.0-2874.0, car test) (eFigure 3D, eTable 3 analysis 24). Automated IED detection in the simulator reduced the trigger latency to 584.5 ms (95%-CI 534.6-674.6) for IEDs without miss/crash ($p < 0.01$, Kruskal-Wallis test; eFigure 3A) and to 701.5 ms (95%-CI 420.0-713.0) for IEDs with miss/crash ($p < 0.01$, Kruskal-Wallis test; eFigure 3D). Trigger latency was normalized by dividing trigger latency by the duration of the associated IED on a session level. This calculation yielded the median occurrence of the stimulus over the time of an IED. For IEDs without miss/crash, these were 0.8 (95%-CI 0.8-0.9) for the flash test, 0.8 (9%-CI 0.7-0.8) for the car test, and 0.7 (95%-CI 0.6-0.7) for the simulator ($p < 0.01$, Kruskal-Wallis test; eFigure 3B, eTable 3 analysis 27). For IEDs with miss/crash, these were 0.5 (95%-CI 0.3-0.7) for the flash test, 0.6 (95%-CI 0.5-0.9) for the car test, and 0.3 (95%-CI 0.2-0.4) for the simulator ($p = 0.01$, Kruskal-Wallis test; eFigure 3E; eTable 3 analysis 25).

To investigate the question of whether a period within IEDs exists that affects behavior most, we analyzed the frequency distribution of misses/crashes during a normalized IED by using normalized trigger latencies to calculate median session miss/crash probabilities$_{IED}$ and

median RT-prolongation of single IEDs for categories of tenths of a normalized IED. To recapitulate, the data analysis criterion that a trigger was fired during ongoing IED, together with normalization of trigger latency, meant that a normalized trigger latency of 0 corresponded to IED onset and a value of 1 corresponded to IED end. This allowed for the definition of a "normalized" IED that could be divided into categories of tenths, corresponding to a normalized trigger latency ranging from 0-0.1, >0.1-0.2, >0.2-0.3, …, and >0.9-1, respectively. Individual IEDs from the 34 sessions with ≥ 1 miss/crash were used to calculate the miss/crash probability for specific tenths of a normalized IED, based on the normalized triggering latency of each individual IED. The total number of misses/crashes were included in the numerator and the total number of stimulus exposures during the IED in the denominator that had a normalized triggering latency within a specified range (e.g., >0.2-0.3) of one of the 10 tenths of a normalized IED. The total number of stimulus exposures in the denominator means that the total number of single IED-RT-prolongations and the number of misses/crashes (which were included in the numerator) were added together, which both had a normalized trigger latency within a given range. How single IED-RT-prolongations were calculated is described in the next chapter. The resulting single IED miss/crash probability distribution per tenths, for all three tests and IED types combined, was skewed towards onset of a normalized IED with a peak miss/crash probability$_{IED}$ of 52.6% in the fourth tenth (>0.3-0.4) (eFigure 3F).

To calculate the distribution of RT prolongation due to single IEDs during a normalized IED, RT prolongations caused by the total number of single IEDs without miss/crash from 148 sessions were approximated. Because stimuli during IED and normal EEG were not paired, the mean RT during normal EEG ($RT_{normal\ EEG}$) of a session had to be subtracted from each RT_{IED} of the same session. The single IED RT-prolongations with a normalized trigger latency within a certain range of the 10 tenths were averaged. As an example, median RT-prolongation ± 95%-CI, resulting from triggering a visual stimulus in the third tenth of a

normalized IED, was obtained by averaging single IED RT-prolongations, coming from all 148 sessions, with normalized trigger latencies ranging from >0.2-0.3. The resulting distribution of median RT-prolongations by single IEDs, calculated for each of the normalized trigger latency ranges, peaked at IED onset (89.9 ms, 95%-CI 49.3-164.5) for the first tenth, showed a trough during the second and third tenths (49.5 ms, 95%-CI 22.8-178.1 and 49.5 ms, 95%-CI 12.2-77.6), had a second minor peak during the fifth tenths (73.3 ms, 95%-CI 55.1-86.2), and gradually decreased toward the end of the IED (eFigure 3C, eTable 3 analysis 28). For all three tests and IED types combined, the third to fourth tenth of a normalized IED contained both a peak in miss/crash probability$_{IED}$ and a trough for RT-prolongation, suggesting that it could impact outcome of the task. We estimated the boundaries of the fourth tenth of an average IED from the dataset in milliseconds by multiplying the respective category of >0.3-0.4 with 1538.5 ms, the median of all individual IED durations. Thus, the fourth tenth of a normalized IED corresponded to ≈462 to ≈615 ms of an average IED (for the three tests and all IED types combined). We have separately calculated the distribution curves according to tenths for each IED type, see eFigure 4, and for each test type (see eFigure 5). One can roughly see a similar distribution of median session miss/crash probability$_{IED}$ and median RT-prolongation of single IEDs for most IED types: a peak in miss/crash probability$_{IED}$ can be observed in the third and fourth tenths while a trough of RT-prolongation can be seen in the third tenth. This trough shifts to the fourth tenth in the focal IED (eFigure 4). Looking at the frequency distribution curve by tenths for each test type, between the third and fourth tenths of a normalized IED, there is a dip in RT-prolongation by single IEDs and a peak in the session probability of miss/crashes (eFigure 5). Particularly the single IED miss/crash probability in the simulator peaks at the third tenth (see also normalized trigger latency in the simulator of 0.29, eFigure 3E).

Discussion

Characteristics of IED behavior on real road that could be replicated using a simulator

Some characteristics of IED behavior on a real road could be replicated by using a simulator. IED frequency per minute of test session decreased in the sequence flash test – car test - simulator. Herewith, our observation confirmed the literature that IED frequency was reduced in patients while driving and increased abruptly when patients waited at traffic lights.[16] In addition, we were able to register sessions with generalized typical IEDs in the simulator, but only containing IEDs without miss/crash. Thus, the simulator as a complex tracking task, i.e., performing a task open eyed with higher cerebral processing load compared to the simple flash and car tests, reduced both the frequency of IEDs/min of test sessions and the number of single generalized typical IEDs with miss/crash. We were not able to record simulator sessions containing generalized typical IED with miss/crash in both adolescents and adults. Also, the duration of IEDs without miss/crash was much shorter in the simulator than in the flash test and car test. All observations were probably due to the same modulatory properties of increased attention performed with open eyes. (i.e., the increased task difficulty of the simulator compared to the flash test and car test). Interestingly, this was not the case for IEDs that resulted in missed reactions, because here the epileptiform discharge seemed to be decoupled from the modulatory property of attention.

The importance of the temporal match of the test task and IED

The length of RT-prolongation and the percentage of miss/crash probability$_{IED}$ depends on the time during an ongoing IED at which the brain is confronted with a test task. This is important because of the transient nature of the IED-associated cognitive impairment which has also been pointed out by previous authors (keyword "spike-locked").[14,15,32,34,41] Thus, the nature of the triggering of a stimulus, and thus the trigger latency, comes to the fore. We recorded a long trigger latency in the manually triggered flash test and in the car test, which was

shortened by using an EEG bandpass filter in combination with an amplitude threshold in the simulator, that is, by automating IED detection, similar to automated spike triggering in other work.[32,34,41] We were probably unable to measure the maximal IED effect on RT-prolongation because the stimuli in all three tests occurred in the last third of the IED, and we were able to show here that the transition from the first to the second third of the IED is a critical range in the brain's compensation for epileptiform discharges, up to which the RT prolongs, only to be either relieved by a miss/crash or to shorten again. The situation was different for IEDs with miss/crash, as these were significantly longer overall and appeared to be less modulated by the incrased task difficulty of the simulator (see previous chapter). In this case, the automatic detection of IEDs and the triggering of stimuli in the simulator led to an optimal match between the appearance of the visual stimulus (normalized trigger latency 0.29, see eFigure 3E) at the time of the maximum miss/crash risk during an ongoing IED (third tenth of a normalized IED, see eFigure 5F). Because of this good temporal match, it can be assumed that the relative risk for IED-related misses/accidents in the simulator translates well to the real road. In future studies, the temporal coincidence of a stimulus or task with an IED will, in principle, no longer be sufficient to determine the maximum impact of IEDs. Real-time IED detection algorithms that can trigger a stimulus or task with a specific latency to present the stimulus or task precisely within the sensitive range of an ongoing IED will likely be required.

A clinically relevant IED

We have calculated a nonlinear relationship between RT-prolongation and the difference in cumulative miss/crash probability between IED and normal EEG to predict an IED with more severe consequences (that is, leading to a missed reaction or crash) as a function of RT-prolongation and to formulate a threshold of concern at which the effects of RT-prolongation and cumulative miss/crash probability could become clinically relevant. We concluded that

RT-prolongation of 150 ms is beyond a threshold of concern for a clinically relevant IED effect, because it was already associated with a 50% cumulative miss/crash probability, that is, if the RT-prolongation of a session is 150 ms, there is a 50% probability that one of the IEDs in the session will cause a miss/crash. The inflection point of the empirical cumulative distribution curve at an RT-prolongation of ≈ 60 ms was associated with ≈ 8% accumulated miss/crash probability, which we considered as too sensitive for a clinically relevant IED effect. In agreement with our previous work,[24] which theoretically proposed a RT-prolongation of 100 ms as potentially clinically relevant (based on the 99th percentile of the standard deviation of a reaction time in healthy young volunteers), and the work of other authors who consider an annual seizure recurrence risk of up to 20% to be consistent with driving (e.g.,[7,8]), we would like to discuss a RT-prolongation of 90.3 ms with a 20% miss/crash risk as a threshold for a clinically relevant IED effect. Gastaut & Zifkin, 1987,[3] investigated which seizure type was most likely to cause accidents while driving. They showed that 88% of epileptic seizures with accidents were caused by complex partial seizures (most without preceding aura) and 7% of seizures were caused by generalized seizures, which can be summarized as seizures with loss of consciousness or impaired awareness. The relation between impaired awareness seizures and IEDs with miss/crash is cognitive impairment. We did not calculate an annual risk for the occurrence of an IED with 20% miss/crash probability, but this might be a starting point for future studies to further define a clinically relevant IED.

Translation of IED-associated effects in our simulator to real-road traffic crash risk in the literature

There are many studies in the laboratory and in real life about the influence of biological factors or environmental factors on driving performance and driving behavior and it is therefore important to choose appropriate studies for the comparison with IED-induced deficits. Studies that are cited here examine the effects of sleepiness, alcohol, and

medications/drugs on driving performance and crashes. It should be noted that the studies on motorized vehicle accidents are retrospective, as are studies that have associated epilepsy or epileptic seizures with relative accident risk (see, e.g.,[8,10]). In such real road association studies, potential confounding factors are generally more difficult to control for than in laboratory studies. In all the studies now listed below, it is probably a good idea, as previously noted by other authors,[e.g.26,27] to express the effects on continuously measurable performance parameters, or on the number of accidents/collisions with a "blood-alcohol equivalent", simply because there are so many studies that have quantified in detail the effect of alcohol on psychomotor performance and driving. Such a systematic study situation is not always given for the other conditions mentioned above, such as sleep and medication intake, so that here, too, the influence of alcohol is often used as a reference. It should be noted that in most countries a blood-alcohol concentration of 0.08% (0.8 per mill) or 0.1% (1 per mill) is the legal limit for fitness-to-drive. Laboratory and real-road studies (for example,[30,40,48]) have shown that much lower blood-alcohol concentrations are already sufficient to cause performance impairment or increase the relative risk for fatal and nonfatal accidents (see below). Thus, when standardizing the effects of drowsiness or IEDs via a "blood-alcohol equivalent", it is important to distinguish whether the goal is to effect a change in policy with legislators (that is, to describe effects that can also be caused by a blood-alcohol concentration of 0.08%), or to achieve safer mobility on the road. Of course, autonomous vehicles are an optional solution for the future. But it will probably be as with other inventions in the history of mankind that both variants, in this case autonomous vehicles and human-controlled vehicles, will co-exist, and one will not be able to deny patients with epilepsy the right to drive a vehicle themselves if they provide the necessary (health) condition.

Let's start with laboratory studies that measured continuous performance parameters and calculated the percentage of performance degradation by blood alcohhol or sleepiness in a

computer tracking task. Dawson et al. presumably (presumably means that it is not explicitly stated) measured the deviation from the ideal line or the crossing of virtual road boundaries. Their study showed that a degradation of tracking performance by 5-10% can be caused by 0.08 % blood-alcohol concentration as well as by >21 h wakefulness.[27] In another study, using a new test that measured lateral deviation of a vehicle on real road,[38] it was shown that an increase in the standard deviation of lateral car position (SDLP) of more than 2.4 cm compared to SDLP in healthy sober drivers can also be caused by a blood-alcohol concentration of 0.05%.[29] This 2.4 cm increase in SDLP was considered a benchmark for future studies that sought to quantify the effects of other factors affecting driving performance via a "blood-alcohol equivalent." For example, in a study investigating common sleep aids on fitness-to-drive. Here, ingestion of 10mg zolpidem at 4 am, 4-5 h before a car trip, resulted in an increase in SDLP of 3.4 cm; ingestion of 15mg zopiclone the evening (approximately 10-11 h) before the car trip resulted in an increase in SDLP of 2.5 cm.[28] For more information on the impact of medications and drugs on motor vehicle crashes, we refer the reader to other studies.[e.g.49,50] We quantified the increase in SDLP, which was 18% for zolpidem and 14% for zopiclone. We attempted to establish a relationship to IED-induced deficits by comparing the relative percent impairment of continuous parameters between studies. In our study, there was an IED-associated relative RT-prolongation of 18% (502.6ms during IED /423.5ms during normal = 1.185) for all epilepsy patients and all test types combined. IED-associated RT-prolongation ranged from 13% for focal IED to 38% for generalized typical IED. A much more appropriate comparison is provided by the study of D. Kasteleijn, 1987, the only one to date that investigated the effect of IEDs on the increase in SDLP while driving on a real road.[39] Of the 6 epilepsy patients studied, three patients, one with generalized epileptiform discharges, and two with focal (bifrontal, or right fronto-temporal) discharges of a median duration between 0.5 and 2 seconds (min 0.2 seconds and max 50 seconds) showed an increase in SDLP of 1.5 cm to 5.2 cm! Thus, it was impressively demonstrated that IEDs can

lead to an increase in SDLP equivalent to and even exceeding the influence of 0.05% blood-alcohol concentration.

The next study cited examined the effects of prolonged wakefulness and blood-alcohol concentration directly on RTs using a computerized response speed test that measured simple RTs.[26] The simple response speed test, which was performed with open eyes on a computer screen, can probably be compared with the car test from our study. RTs ranged from 489 – 494 ms in fasting and rested patients,[33] while in our car test, median RTs were around 474 ms during normal EEG. A blood-alcohol concentration of 0.05% prolonged RTs to 534 ms (+45 ms), and a blood-alcohol concentration of 0.1% prolonged RTs to 566 ms (+77 ms). RT-prolongation by 45 ms was caused by prolonged wakefulness of 18 hours (95%-CI 17.1-19.0 h), and RT-prolongation by 77 ms could be caused by slightly longer wakefulness (95%-CI 17.6-19.9 h).[26] In our sessions with the car test, RT was prolonged by a median 76 ms when all IEDs were combined. Thus, under laboratory conditions, IED effects on simple RT could be compared with a blood-alcohol concentration of 0.05-0.1% or to wakefulness of > 18 hours.

Let us now turn to the studies with driving simulator collisions and real-road crashes. Comparison with these studies is likely to futher clarify the translation of potential IED effects to daily life activities. Several laboratory studies have already been conducted on the impact of IEDs on missed responses. For example, the studies by Shewmon et al. quantified the impact of focal IEDs (some lasting up to 700ms) on missed responses and RTs,[32] or proved the neuroanatomical specificity of IEDs.[34] The aim of our study was not to replicate these findings, but to take the effects of IEDs to another, more practical level, namely that decisions about EEG compatibility for the fitness-to-drive can be individualized for patients using the techniques and guides presented in our manuscript on the one hand, and standardized and internationalized with respect to practices at different epilepsy clinics on the

other. As with the studies cited above, the influence of wakefulness or drowsiness, respectively, and alcohol on collision or accident counts was investigated both in the laboratory and on real roads. There are several studies on this topic. We would like to limit our information here to two studies, both of which were conducted on behalf of the U.S. Department of Transportation. The reasons for our choice are that due to the government as sponsor, a relevant study size, experience in planning and implementation, and thorough statistical evaluation can be assumed. In 2000, a driving simulator study was conducted for the U.S. Department of Transportation in Washington, DC, to investigate the effects of blood-alcohol concentration on various parameters such as lane departure, RT, and number of collisions.[40] The number of collisions was standardized by calculating the log odds of the number of collisions with various blood-alcohol concentrations minus log odds of the number of collisions while driving sober in the simulator (pre-treatment). The log odds values ranged from approximately 0.1 with 0.02% blood-alcohol concentration to a log odds to 1 with 0.1% blood-alcohol concentration. In our study with the simulator, the odds ratio was 4.9 (95%-CI 1.5-16.1) to cause a miss/crash during IED compared with a miss/crash during normal EEG. The log odds for the simulator data were were 1.58 (95%-CI 0.4-2.8). Because in our study all patients served as their own controls and we examined only one parameter, IED, subtraction of log odds (log odds IED - log odds normal) was not necessary. The mean participant age in the Moskowitz study was 33 yrs. 2 mo. for women and 34 yrs. 11 mo. for men with exactly the same number of female participants and male participants (84 each). The mean age and standard deviation in our study was 32 yrs. 3 mo. (15yrs. 3 mo.) for women and 33yrs. 4 mo. (16 yrs. 11 mo.) for men in 48 women and 47 men with epilepsy. A possible confounding factor in the comparison of both log odds values could be that in the Moskowitz study all participants received 2x 4 h training sessions before the actual experiments, whereas our patients were driving in a driving simulator for the first time when the influence of IEDs on RTs and miss/crash was measured. A conservative comparison of log odds values from both

studies suggests that the influence of IEDs on miss/crash in the simulator is not inferior to the influence of 0.1% blood-alcohol concentration.

Another study for the U.S. Department of Transportation, Washington, DC, in 2000 re-examined the alcohol-related relative risk of driver involvement in fatal crashes by age and sex as a function of BAC using recent real-road data.[30] Among other things, the relative risk of a single vehicle accident (only 1 person in the car) with a fatal outcome or without a fatal outcome (crash involvement) was examined. It was shown that single vehicle accidents correlate best with blood-alcohol concentration. The relative risk was approximated by the odds ratio. The odds ratios themselves were obtained by exponentiating the coefficients from a logistic regression model. The crash risk under alcohol was compared with that of sober drivers (mathematically, the frequency of fatal and nonfatal crashes with 0.0% blood-alcohol concentration divided by the number of (exposed) drivers interviewed and tested for alcohol in systematic surveys (National Roadside Survey)). Across all age groups and sex groups, the odds ratio (the approximated relative risk) for a fatal injury crash was increased by a factor of 2.6-4.6 at a blood-alcohol concentration of 0.035% (these are not confidence intervals but the ranges of odds ratios across age groups). The relative driver involvement risk (omitting fatal outcome) was increased by a factor of 2.3-3.9 with a blood-alcohol concentration of 0.035% (2.3 for road users >20 yrs. of age, 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 of 16-20 yrs). In our study with th stimulator, as mentioned above, the odds ratio in the simulator was increased by a factor of 4.9 to suffer a miss/crash during IED compared with normal EEG. As mentioned, miss/crash also occurred during normal EEG, most likely due to a lack of attention. In the study by Zador et al, road users between 16 and 20 years of age had a significantly higher odds ratio (approximated relative risk) of causing a crash with or without a fatal outcome than all other road users older than 20 years. This dichotomy of results based on age groups could not be reproduced in the simulator in our

epilepsy patients. The odds ratio was not increased in the simulator in patients 14-17 yrs. compared with patients ≥18 yrs. For comparison, in addition to the odds ratio, we also calculated the IED-associated relative risk for miss/crash, which was increased by a factor of 2.7 (95%-CI 1.3-4.1) in the simulator, and *4.1-fold* (95%-CI 3.8-4.4) *in all test types* (that is, data from the flash, car test, and simulator combined). In summary, our data can be cautiously translated as follows: as far as comparable in the mathematical assessments, the relative risk for epilepsy patients of all age and gender groups to suffer a miss/crash during IED in the simulator is increased by a comparable factor as to cause a collision in the driving simulator with 0.05%-0.1% blood-alcohol concentration, and as to be involved in a single-vehicle crash on real road with 0.035% blood-alcohol concentration.

Another comparison that is always made to laboratory studies with epilepsy patients is whether the effects of IEDs can be compared to drowsiness and/or microsleep in everyday situations. According to our search, there are no studies that have examined the relative risk or odds ratio of microsleep as a cause of traffic accidents. However, there are some studies on drowsiness and accidents in the laboratory and on the road. I would like to refer here to a 2017 meta-analysis that included almost 70000 road users from different studies.[31] One outcome parameter was a two- or four-wheeled motor vehicle accident by participants with and without sleepiness while driving on a real road. We use the terms drowsiness and sleepiness synonymously here (the term sleepiness was used by the meta-analysis). Sleepiness at the wheel was self-reported. The inclusion criterion for sleepiness was variably defined in the different studies that were summarized in this meta-analysis, and ranged for example from "almost falling asleep while driving", to surveys with a sleepiness severity scale 4-7, and to "at least one episode of severe sleepiness at the wheel in the previous year". Risk estimates and 95%-CI were extracted from the studies and pooled as odds ratios. The pooled odds ratio of suffering a motor vehicle accident during sleepiness at the wheel was increased by a factor of 2.5 (95%-CI 1.9-3.4). Because the range of drowsiness definitions is broad, a higher odds

ratio for accidents due to drowsy driving can be assumed. However, in summary, this result fits the laboratory studies with prolonged wakefulness,[26,27] and the effects can be roughly compared to a blood-alcohol concentration of 0.05%. Thus, the drowsiness-associated relative risk of accidents does not exceed the potential effects of IEDs.

Decision aid for fitness-to-drive evaluation

The following examples should illustrate the use of the decision aid.

During a routine outpatient examination, a patient presents and reports that all is well and that no seizure has occurred in the last 6 months. A standard surface EEG is performed and IEDs stand out. The decision aid was created to identify potentially relevant IEDs by associating morphology and duration criteria with expectable IED-induced deficits. The following information should support the treating physician in evaluating the EEG outcome for fitness-to-drive and in determining whether further testing will provide additional certainty in deciding about driving ability. Although RT-prolongations and miss/crash probabilities due to single IED-bursts were mapped to IED type and duration-intervals, it is not recommended to base the evaluation on individual IEDs, but to assess the predominant morphology (type) of IEDs and to calculate the average IED duration of the routine EEG. By doing so it is made sure that the majority of IEDs in the respective routine EEG are of a particular type and duration. This also ensures a higher probability that a potentially clinical relevant IED occurs with higher frequency. It is also recommended to determine the IED frequency by calculating the number of IEDs per minute of EEG recording. Using now the decision aid (table 2), the expected RT-prolongation or miss/crash probability can be determined.

The application of the decision aid is now illustrated using three fictious examples. In the first first example, a patient has structural epilepsy and focal IEDs. Irrespective of the configuration of epileptiform potentials, if the focal IED-bursts have an average duration of

morer than 2 seconds, these IEDs may be associated with a miss/crash in rare cases, even if the associated RT-prolongation is small. This patient is recommended to undergo additional testing, for example with a reaction test or tracking test, if available.

In the second example, a patient has epilepsy of unknown origin with both focal and generalized IEDs. The generalized IEDs predominate, moreover, the amplitude of the epileptiform bursts decreases during the IED, the potentials often appear plump, no proper after-going wave is seen, in summary, this type of IED is classified as generalized atypical. Also, in this case the average duration of all recorded IEDs is calculated and is about 2 seconds. That is, this patient has generalized atypical IEDs in the 1000-3000ms duration-interval. With this IED type and duration, a RT-prolongation of 50ms and a miss/crash probability of 2.1% can be expected. Considering that the probability of miss/crash due to inattention during a normal EEG period is less than 1%, this patient could have a ≈ 2-fold increased risk (conservative estimate) for a miss/crash with this IED type. It may still be uncertain whether the IED-induced deficit to be expected is severe enough to respond with a change in medication or recommend fitness-to-drive testing. In this case, it may be helpful to consult the IED frequency for decision making. In our dataset, an IED occurred on average every two minutes in sessions that were classified as generalized atypical, resulting in an IED frequency of 0.5/min (see figure 2A). An IED frequency of greater than one burst every two minutes (greater than 0.5/min) in the routine EEG of our example patient, that is the prevalence of IEDs is occasional to frequent, would argue in favor of further fitness-to-drive testing. Any circadian rhythm effect on the frequency of IEDs can be at least partially controlled by testing in the late morning or afternoon, but in any case, not in the early morning, evening, or peri prandially (to compare with our dataset).

Third, for long generalized IEDs with an average duration of more than 3 seconds, fitness-to-drive testing is recommended regardless of epilepsy type. It is also often difficult to classify

an EEG as with predominantly generalized atypical IEDs or with generalized typical IEDs. Interrater variability is likely to be high. In addition, the epileptiform potentials of idiopathic epilepsies, such as absence epilepsy, when generalized epileptiform discharges persist into adulthood, may be modulated in their appearance by antiseizure medication to the extent that they could no longer be classified as generalized typical. For this reason, this recommendation does not distinguish between generalized atypical IEDs and generalized typical IEDs, but recommends fitness-to-drive testing, if possible, in the event that generalized IEDs with an average duration of more than three seconds are detected in the respective routine EEG.

eMethods

Patients

To maximize the number of subjects that could be included, and since we wanted to compare between the three test types and between the 2 age groups (adults and adolescents), we decided to include both data from 41 subjects recruited between 2015 and 2018, as well as previous data from our research group,[23,24] to perform a meta-analysis. $RT_{normal\ EEG}$, RT_{IED}, trigger latencies, and IED duration from the car test and the flash test were included from 23 adults' sessions published in Krestel et al. Epilepsia 2011,[23] (listed in eTable 1 as Epi11) and from 40 adults' sessions published in Nirkko et al. Epilepsia 2016,[24] (listed in eTable 1 as Epi16). Crashes from the car test sessions in both studies were also included. The prior definition of a lapse (RT ≥ 1000 ms) in the flash test was abandoned and the concept of a missed reaction was newly introduced. A missed reaction was defined as no response at any latency. This concept distinguishes more clearly between events with severe behavioral impairment (no response) and events with normal or milder impairment (normal or delayed RT). The datasets of both previous studies were reanalyzed and RTs ≥ 1000 ms that were previously defined as lapses were assigned to either $RT_{normal\ EEG}$ or RT_{IED}. Missed reactions were only cases in which there was no response to a stimulus.

Reaction tests

Effects of IEDs on the ability to respond were assessed with a flash test, car test, and a realistic driving simulator while a routine 10/20 scalp EEG was recorded. Typical test session duration was 16-30 minutes. Visual stimuli were manually triggered in random fashion during normal EEG in all three tests, and as soon as each IED was recognized in the flash test and the car test.[23,24] In the realistic driving simulator only, IED detection and stimulus triggering was automated using an algorithm prototype.[51] Each patient served as their own individual control,

as RTs and misses/crashes were measured during both normal EEG and IEDs. Patient response was by manual button-press in the flash test and car test, and by right-foot brake in the simulator. We used the same technique for the flash test and car test as employed in our previous studies:[23,24] the car test was previously named steer clear.[23] A realistic driving simulator (F12PF, Foerst, Germany) was employed for the first time in this study. The F12PF driving simulator consisted of a half-cab with a steering wheel, gas and braking pedals. Several parameters could be recorded including steering wheel angle, speed, and braking distance. We decided to analyze speed and total stopping distance. We believed that these parameters could be better transferred to a real-road situation, and that they could be understood more easily, both by patients who had completed a driving simulator session and by policy makers of fitness-to-drive evaluations, than the parameter RT-prolongation. "Driving on empty highway at night" was chosen as the driving scenario, because it was uneventful and should decrease distraction as well as improve patient compliance with the instructions to keep speed constant at 100 km/h (≈62 mph) and to brake fully upon stop sign appearance. Red stop signs were projected with a beamer in front of the driver and were randomly triggered during normal EEG by research staff with a mouse-click on the computer running the driving scenario. IEDs were detected using a self-programmed and patented algorithm running on a custom-made device.[51] For the flash test and car test, we had used a Natus amplifier (Nicolet, Natus Incorporated, USA). For the simulator, we decided to use a different amplifier, Trackit (mk3, Lifelines Ltd, Hants, UK), as its communication protocol with the computer was available, allowing us to automate IED detection and stimulus triggering. Because of the limited working memory of the Raspberry Pi, we removed 9 of the 20 scalp electrodes used for EEG recordings in the flash test and car test. The 11 remaining electrodes were: frontal (F3, F4), central (C3, C4), temporal (T3, T4), parietal (P3, P4), and occipital (O1, O2), with FCz as the reference electrode. The electrode montage remained according to the 10-20 system. The algorithm ran on a custom-made device ("iRT," built by

AvA) consisting of a microcontroller and single-board computer (Raspberry Pi) with a Linux operating system. iRT additionally performed EEG signal processing from Trackit, started an internal clock by input from a photo-voltaic sensor when it registered on-screen stop sign appearance, and stopped the clock when braking occurred (through input from a pressure sensor on the braking pedal). EEG signals and square wave signals in auxiliary EEG channels indicating stimulus triggering, detection of on-screen stimulus appearance, and time to braking were displayed by iRT in real-time on a monitor. Speed and total stopping distance were recorded by the computer in the simulator cab. The time between stimulus triggering and detection of on-screen stimulus appearance was the digital latency of the serial electronic devices (computer running the driving simulation and triggering the stop sign, computer network, beamer). This digital latency was a median 234 ms (min. 190 ms, max. 611 ms) and had a skewed distribution, which necessitated measuring onscreen stimulus appearance with a photo-voltaic sensor to circumvent digital latencies generated by the electronic devices and record RT from the moment stimuli could be perceived by the patients.[52]

Study parameters

Calculation of miss/crash probability$_{\text{normal EEG}}$, single IED miss/crash probability, and single IED RT-prolongation

Missed reactions (flash test, simulator) or crashes (car test) occurred not only during IEDs but occasionally during segments with normal EEG. Here, the miss/crash probability during periods of normal EEG of a test session (miss/crash probability$_{\text{normal EEG}}$) was calculated in an analogous manner to session miss/crash probability$_{\text{IED}}$, namely as the number of missed reactions or crashes during normal EEG divided by the number of visual stimuli triggered during normal EEG of that session.

A single IED-burst miss/crash probability was calculated by dividing, for example, all 102 miss/crashes registered in the meta-analysis by all visual stimuli during IEDs (2207). For a

particular IED type or test type, the number of miss/crashes was divided by the number of stimuli during the IEDs from all sessions classified with that IED type or conducted with that test (independent of sessions). In other words, the classification of single IED-burst miss/crash probability by an IED type or a test type was based on the classification of the session from which the IEDs with miss/crash and the IEDs without miss/crash originated or the test used to conduct the session. The underlying concept is based on clinical practice regarding the evaluation of EEGs and on the basic assumption that the predominance of one IED type shapes the entire session in terms of reactivity and behavior in the sense of an intrinsic biological feature. To estimate RT-prolongation by individual IEDs, the mean RT during normal EEG from a session was subtracted from the RTs during each IED from the same session. This was necessary because RTs were not paired but there were much more RTs during normal EEG than during IEDs in a session. Classification of RT-prolongations of single IEDs by an IED type was based on the classification of the session from which the IEDs originated.

Cumulative distribution function to relate miss/crash probability with RT-prolongation

The difference in miss/crash probability between IED and normal EEG, and RT-prolongation were related on a session level using a cumulative distribution function. Mean differences in miss/crash probability between IED and normal EEG, and mean RT-prolongations of the 34 study sessions with ≥ 1 IED-associated miss/crash were listed in a table. These sessions represented data from 27 patients and all three tests. The table was sorted by length of mean RT-prolongation in ascending order (min. 6.6 ms, max. 655 ms). Next, each difference in miss/crash probability between IED and normal EEG was divided by the sum of the differences in miss/crash probability between IED and normal EEG, resulting in relative differences in miss/crash probability between IED and normal EEG that added up to 1 or 100%. Relative differences in miss/crash probability were grouped into rising quantile bins of

RT-prolongation. Bins were of 10ms duration with class limits of 1-10 ms, >10-20 ms, ... up to >650-660 ms. By combining these bins, new bins were defined by class limits of 1-10, 1-20, 1-30 etc. up to 1-660. The cumulative differences in miss/crash probability between IED and normal EEG were defined for these bins by summing the relative differences in miss/crash probability of sessions that had mean RT-prolongation in these duration ranges. Cumulative differences in miss/crash probability between IED and normal EEG allowed for the data to be represented as a probability distribution (i.e., an empirical cumulative distribution function). For a particular RT-prolongation *X*, the accumulated difference in miss/crash probability between IED and normal EEG was the sum of the relative differences in miss/crash probability for the range of RT-prolongations from 1 ms up to *X*.

Non-linear fit to accumulated miss/crash probability in relation to RT-prolongation

A non-linear least squares regression curve was fitted to the discrete data of accumulated differences in miss/crash probability between IED and normal EEG in relation to RT-prolongation ($R^2 = 0.99$, Kolmogorov-Smirnov test $p < 0.01$). This relationship was modeled using the Gompertz growth curve in Prism 9 with the following equation:

$$y = 0.8902 * (\frac{0.001488}{0.8902})^{exp\,(-\frac{x}{62.09})}$$

The first inflection point of the fit was determined with GraphPad Prism 9; it indicated the RT-prolongation at which the accumulated difference in miss/crash probability started to rise more strongly (i.e., where the fit transitioned from concave to convex shape). At this inflection point, the accumulated difference in miss/crash probability was determined with Desmos[53] to be 8.5%. The RT-prolongation associated with an accumulated difference in miss/crash probability of 50% was also determined using Desmos.

Equation[54] for calculating total stopping distance

$$S_{tot} = v_0\ (\mathrm{RT}\ +\ t_S) - \frac{1}{6} a {t_S}^2\ + \frac{\left(v_0 - \frac{a}{2} t_S\right)^2\ -\ {v_T}^2}{2a}$$

S_{tot} = total stopping distance; v_0 = initial speed; v_T = terminal speed; RT = reaction time; t_S= brake pressure build-up time (time between beginning of and maximal mean car delay, typically 0.2-0.4 s for a passenger car, set to 0.2 s); a = braking deceleration, set to 7.5 m/s^2.

Purpose of each statistical analysis including null hypothesis (H_0), state if the data are paired or unpaired, and if repeated measures analysis were used

The Mann-Whitney *U* Test (hereafter called Mann-Whitney test) was used to compare the distributions of two unpaired groups:

- IED-associated RT-prolongation between male and female participants and between left-and right-hemispheric focal IEDs of all participants (null hypothesis H_0: IED-associated RT-prolongation does not differ between males and females (eAppendix 1 p.3, eTable 3 analysis 10) and between left- and right-hemispheric focal IEDs, given that patients with focal epilepsy and IEDs in the left hemisphere are different individuals than patients with focal epilepsy and IEDs in the right hemisphere and thus also the variable "ΔRT left" is independent from the variable "ΔRT right" (main text p.11, eTable 3 analysis 11)).
- Durations of IEDs without miss/crash from 148 sessions compared to durations of IEDs with miss/crash from 34 sessions (H_0: durations of IEDs without miss/crash, taken from 148 sessions, do not differ from durations of IEDs with miss/crash, taken from 34 sessions; figure 4A, main text p.11, eTable 3 analysis 20).
- IED frequency per minute from 148 sessions, divided into 121 sessions that contained only IEDs without miss/crash, and 27 sessions that contained both IEDs with miss/crash and without (H_0: the presence of an IED with miss/crash in a session does

not affect the session IED frequency, given in 1/min; main text p.14, eTable 3 analysis 59).

- Duration of single IED-bursts without miss/crash from 121 sessions that only contained IEDs without miss/crash compared to the duration of single IED-bursts without miss/crash of 27 sessions that contained IEDs with miss/crash and without (H_0: the duration of single IED-bursts without miss/crash from 121 sessions containing only IEDs without miss/crash is not different from the duration of IEDs without miss/crash from 27 sessions containing IEDs with miss/crash and without; main text p.14, eTable 3 analysis 60).
- Measured speed, measured total stopping distance, and calculated total stopping distance in the driving simulator during IEDs and during normal EEG (H_0: the individual measurements of speed, total stopping distance, and the calculated total stopping distance do not differ between the IEDs, which are much less frequent in the respective test sessions, and the much more frequent sections with normal EEG; eAppendix 1 p.5, eFigure 2A, eTable 3 analyses 50-52).

The Wilcoxon signed-rank test (hereafter abbreviated Wilcoxon test) was used to compare the distributions of two paired groups:

- RT pairs of normal EEG vs. IED EEG on a session level (H_0: $RT_{normal\ EEG}$ and RT_{IED}, determined for each session, do not differ; table 1, eTable 3 analysis 1).
- session miss/crash probability pairs of normal EEG vs. IED EEG (H_0: session miss/crash $probability_{normal\ EEG}$ is not different from session miss/crash $probability_{IED}$; table 1, eTable 3 analysis 2).

- RT pairs (Normal, IED) of sessions using the flash test (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session with the flash test; table 1, eTable 3 analysis 29).
- RT pairs (Normal, IED) of sessions using the car test (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session with the car test; table 1, eTable 3 analysis 31).
- RT pairs (Normal, IED) of sessions using the simulator (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session with the simulator; table 1, eTable 3 analysis 33).
- RT pairs (Normal, IED) of adolescents using the flash test (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adolescents were tested with the flash test; table 1, eTable 3 analysis 38).
- RT pairs (Normal, IED) of adolescents using the car test (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adolescents were tested with the car test; table 1, eTable 3 analysis 39).
- RT pairs (Normal, IED) of adolescents using the simulator (H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adolescents were tested with the simulator; table 1, eTable 3 analysis 40).
- RT pairs (Normal, IED) of adults using the flash test ((H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adults were tested with the flash test; table 1, eTable 3 analysis 42).
- RT pairs (Normal, IED) of adults using the car test ((H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adults were tested with the car test; table 1, eTable 3 analysis 43).
- RT pairs (Normal, IED) of adults using the simulator ((H_0: mean RT_{IED} is not different from mean $RT_{normal\ EEG}$ of each session when the adults were tested with the simulator; table 1, eTable 3 analysis 44).

- Measured total stopping distance pairs in adolescents of normal EEG vs. IED EEG (H_0: the measured total stopping distance in the simulator, determined for normal EEG and IEDs in each test session completed by adolescents, does not differ; eAppendix 1 p.5, eTable 3 analysis 53).
- Measured total stopping distance pairs in adults of normal EEG vs. IED EEG (H_0: the measured total stopping distance in the simulator, determined for normal EEG and IEDs in each test session completed by adults, does not differ, eAppendix 1 p.5, eTable 3 analysis 54).
- Calculated total stopping distance pairs in adolescents of normal EEG vs. IED EEG (H_0: the calculated total stopping distance in the simulator obtained for normal EEG and IEDs in each test session completed by adolescents does not differ; eTable 3 analysis 58).
- Calculated total stopping distance pairs in adults of normal EEG vs. IED EEG (H_0: the calculated total stopping distance in the simulator obtained for normal EEG and IEDs in each test session completed by adults does not differ; eTable 3 analysis 58).
- Measured reaction distance pairs in adolescents of normal EEG vs. IED EEG (H_0: the measured braking distance in the simulator, determined for normal EEG and IEDs in each test session completed by adolescents, does not differ; eAppendix 1 p.6, eFigure 2C, eTable 3 analysis 63).
- Measured reaction distance pairs in adults of normal EEG vs. IED EEG (H_0: the measured braking distance in the simulator, determined for normal EEG and IEDs in each test session completed by adults, does not differ; eAppendix 1 p.6, eFigure 2C, eTable 3 analysis 64).
- Calculated reaction distance pairs in adolescents of normal EEG vs. IED EEG (H_0: the measured braking distance in the simulator, determined for normal EEG and IEDs in

each test session completed by adolescents, does not differ; eAppendix 1 p.6, eFigure 2E, eTable 3 analysis 67).

- Calculated reaction distance pairs in adults of normal EEG vs. IED EEG (H_0: the measured braking distance in the simulator, determined for normal EEG and IEDs in each test session completed by adults, does not differ; eAppendix 1 p.6, eFigure 2E, eTable 3 analysis 68).

The Kruskal-Wallis *H* test (hereafter called Kruskal-Wallis test) was used to compare the distributions of three unpaired groups:

- Session RT-prolongation grouped according to IED type (H_0: RT-prolongation (RT_{IED} - $RT_{normal\ EEG}$) of each session does not differ between sessions that were classified to contain focal IEDs, generalized atypical IEDs, or generalized typical IEDs; main text p. 10, eTable 3 analysis 5). Sessions classified to contain predominantly focal IEDs, generalized atypical IEDs, or generalize typical IEDs are independent from each other.
- Session miss/crash $probability_{IED}$ grouped according to IED type (H_0: session miss/crash $probability_{IED}$ does not differ between sessions that were classified to contain focal IEDs, generalized atypical IEDs, or generalized typical IEDs; main text p. 10, eTable 3 analysis 7).
- Duration of IEDs without miss/crash grouped according to IED type (H_0: the duration of IEDs without miss/crash determined for each session did not differ between sessions that were classified as having predominantly focal IEDs, generalized atypical IEDs, or generalized typical IEDs; main text p.10, eTable 3 analysis 6).
- Duration of IEDs with miss/crash grouped according to IED type (H_0: the duration of IEDs with miss/crash determined for each session did not differ between sessions that

were classified as having predominantly focal IEDs, generalized atypical IEDs, or generalized typical IEDs; main text p.11, eTable 3 analysis 9).

- Session RT-prolongation grouped according to test type (flash test, car test, simulator) (H_0: session RT-prolongation is independent of the test type used; main text p.11, eTable 3 analysis 15).
- RT-prolongation of sessions using the flash test, grouped according to IED type (H_0: RT-prolongation of sessions using the flash test is independent of the IED type; table 1, eTable 3 analysis 30)
- RT-prolongation of sessions using the car test, grouped according to IED type (H_0: RT-prolongation of sessions using the car test is independent of the IED type; table 1, eTable 3 analysis 32).
- RT-prolongation of sessions using the simulator, grouped according to IED type (H_0: RT-prolongation of sessions using the simulator is independent of the IED type; table 1, eTable 3 analysis 34).
- Session RT-prolongation of adolescents, grouped according to test type (H_0: session RT-prolongation of adolescents is independent of the test type used; eAppendix 1 p.4, eTable 3 analysis 48).
- Session RT-prolongation of adults, grouped according to test type (H_0: session RT-prolongation of adults is independent of the test type used; eAppendix 1 p.4, eTable 3 analysis 48).
- Session miss/crash probability$_{IED}$ grouped according to test type (H_0: session miss/crash probability$_{IED}$ is independent of the test type used; main text p.11, eTable 3 analysis 17).
- Miss/crash probability$_{IED}$ of sessions using the flash test, grouped according to IED type (H_0: miss/crash probability$_{IED}$ of sessions using the flash test is independent of the IED type; table 1, eTable 3 analysis 35).

- Miss/crash probability$_{IED}$ of sessions using the car test, grouped according to IED type (H_0: miss/crash probability$_{IED}$ of sessions using the car test is independent of the IED type; table 1, eTable 3 analysis 36).
- Miss/crash probability$_{IED}$ of sessions using the simulator, grouped according to IED type (H_0: miss/crash probability$_{IED}$ of sessions using the simulator is independent of the IED type; table 1, eTable 3 analysis 37).
- Session miss/crash probability$_{IED}$ of adolescents, grouped according to test type (H_0: session miss/crash probabilityIED of adolescents is independent of the test type used; eAppendix 1 p. 4, eTable 3 analysis 49).
- Session miss/crash probability$_{IED}$ of adults, grouped according to test type (H_0: session miss/crash probabilityIED of adults is independent of the test type used; eAppendix 1 p. 4, eTable 3 analysis 49).
- Duration of IEDs without miss/crash grouped according to test type (H_0: the duration of IEDs without miss/crash determined for each session is independent of the test type used; main text p.11, eTable 3 analysis 16).
- Duration of IEDs with miss/crash grouped according to test type (H_0: the duration of IEDs with miss/crash determined for each session is independent of the test type used; main text p.11, eTable 3 analysis 19).
- Frequency of IEDs without miss/crash per min of sessions grouped according to test type (H_0: frequency of IEDs without miss/crash per minute of session is independent of the test type used; figure 3A, eTable 3 analysis 14).
- Frequency of IEDs without miss/crash per min of sessions grouped according to IED type (H_0: frequency of IEDs with miss/crash per minute of session is independent of the IED type; figure 2A, eTable 3 analysis 4).

- Trigger latency of IEDs without miss/crash, grouped according to test type (H_0: the trigger latency for IEDs without miss/crash is independent of the test type used; eFigure 3A, eAppendix 1 p.7, eTable 3 analysis 26).
- Trigger latency for IEDs with miss/crash, grouped according to test type (H_0: the trigger latency for IEDs with miss/crash is independent of the test type used; eFigure 3D eAppendix 1 p.7, eTable 3 analysis 24).
- Normalized trigger latency of IEDs without miss/crash, grouped according to test type (H_0: normalized trigger latency for IEDs without miss/crash is independent of the test type used; eFigure 3B, eAppendix 1 p.8, eTable 3 analysis 27)
- Normalized trigger latency for IEDs with miss/crash, grouped according to test type (H_0: normalized trigger latency for IEDs with miss/crash is independent of the test type used; eFigure 3E, eAppendix 1 p.8, eTable 3 analysis 25).
- Session RT-prolongation of adolescents grouped according to test type (H_0: session RT-prolongation of adolescents is independent of the test type used; eAppendix 1 p.3, eTable 3 analysis 41).
- Session miss/crash probability of adolescents grouped according to test type (H_0: session miss/crash probability of adolescents is independent of the test type used; eAppendix 1 p.3-4, eTable 3 analysis 46)
- Session RT-prolongation of adults grouped according to test type (H_0: session RT-prolongation of adults is independent of the test type used; eAppendix 1 p.4, eTable 3 analysis 45).
- Session miss/crash probability of adults grouped according to test type (H_0: session miss/crash probability of adults is independent of the test type used, eAppendix. 1 p.4, eTable 3 analysis 47).

- Peak IED frequency on a session level of all 155 sessions grouped according to IED type (H_0: Session peak IED frequency is independent of the IED type; eAppendix 1 p.2, eTable 3 analysis 71).
- Peak IED frequency on a session level of all 155 sessions grouped according to test type (H_0: Session peak IED frequency is independent of the test type used; eAppendix 1 p.2, eTable 3 analysis 72).

The Friedman test was not used in this study because we did not compare three or more paired groups at a time point, nor did we make multiple measurements in a time series for the same variable (see also the response to major comment 4).

The Chi-square test was used to compare:

- Miss/crash probability during normal EEG compared to IED for all patients and tests (H0: miss/crash probability does not differ between periods of normal EEG and IEDs; table 1, eTable 3 analysis 3).
- Single IED-burst miss/crash probability grouped according to IED type (H_0: single IED miss/crash probability is independent of the IED type; figure 2E, main text p.10, eTable 3 analysis 8).
- Single IED-burst miss/crash probability grouped according to test type (H_0: single IED miss/crash probability is independent from the test type used; figure 3E, main text p.11, eTable 3 analysis 18).

The Fisher's exact test was used to compare:

- The single IED-burst miss/crash probability is compared between female and male participants (H_0: there is no gender difference in single IED miss/crash probability; eAppendix 1 p.3, eTable 3 analysis 12).

The Odds ratio and the relative risk were used to quantify the association between the ratio of miss/crash divided by all stimuli recorded during normal EEG and the ratio of miss/crash divided by all stimuli observed during IED (figure 4C, main. text p.12, eTable 3 analysis 22).

The empirical cumulative distribution function was used to determine the best inflection point of the difference in cumulative miss/crash probability between IED and normal EEG as a function of RT prolongation, and to differentiate miss/crash probabilities between different IED types (eMethods p.4).

The Nested Ranks Test was used to verify the exploratory comparison of adolescents and adults regarding the measured total stopping distance during normal EEG and IED (eTable 3 analysis 56).

Simple linear regression was used to:

- Analyze the difference in stopping distance between IED and normal EEG as a function of the difference in driving simulator speed between IED and normal EEG. Data were paired as the mean values of 30 sessions, equal to 30 patients, and were entered into the regression (eAppendix 1 p.5, eTable 3 analysis 57).

- Present the relation of peak IED frequency with RT-prolongation on a session level. Because it was not verified that the data met the assumptions of simple linear regression, the relation of the data was only displayed so that they can be visually inspected, and R^2 was calculated (eTable 3 analysis 73).

A nonparametric permutation test was used to compare the bivariate data of measured reaction distance during normal EEG and IED between adolescents and adults (eAppendix 1 p.6, eFigure 2C, eTable 3 analysis 69). The Euclidean distance between the bivariate means was chosen as a test statistic. The same test was applied for comparison of the bivariate data of calculated reaction distance (eAppendix 1 p.6, eFigure 2E, eTable 3 analysis 70).

Treatment of missing variables in the analyses and control of confounding variables

1.1% of values were missing for trigger latency and 0.5% for IED duration. These missing values occurred because in the first post-hoc analysis of the EEG after the experiments, trigger latency or IED duration was forgotten to be measured in individual cases. This could be made up later in a second round, except for some EEGs where there was a server problem in the clinic and a few EEGs were lost. 4% of speed and braking distance measurements during IEDs were missing in one patient due to technical reasons during the driving simulator test session. There were no missing values for the other variables. Importantly, no missing data occurred among the outcome variables RT-prolongation and miss/crash. Trigger latency is not a predictor for the two main outcome variables of the study. IED duration is a certain predictor for miss/crash, because IEDs associated with a miss/crash have longer durations than IEDs not leading to a miss/crash, that is to RT-prolongation. The missing values of IED duration did not depend on the outcome or other predictors without missing values. In

summary, all missing values did not depend on either observed or unobserved data. We therefore found no evidence for missing at random (MAR) data or missing not at random (MNAR) data and concluded that the assumptions for data missing completely at random (MCAR) were met. No data were imputed in the study. For statistical testing, cases for which a value was missing were deleted list-wise (or row-wise, respectively). For example, for the patient who drove the simulator and for whom, for technical reasons, speed and stopping distance could be measured during normal EEG but not during IEDs, mean speed and mean stopping distance during normal EEG were deleted for the purpose of pairwise statistical testing.

Potential confounders were controlled by the study design and statistical analysis using post-hoc ANCOVA. Each patient served as her or his intraindividual control, thereby controlling for possible confounding effects on the outcome variable RT-prolongation. This study did not include healthy controls who might still have to be matched with the epilepsy patients. Patients with early epileptic encephalopathy were excluded to avoid possible effects on slow reaction times and increased error rates due to disease-related factors other than IEDs. Possible confounding factors for the main outcome variables RT-prolongation and miss/crash include age, sex, number of antiseizure medication (ASM) taken, (slow) reaction time during normal EEG for various medical reasons, and inhomogeneity of diurnal testing conditions. No significant sex-specific differences in RT-prolongation and miss/crash were found, as reported in analyses 10 and 12 on eTable3. We previously showed that the number of ASMs taken slowed RT during normal EEG. We found, however, no correlation between RT during normal EEG (which was affected by the number of ASMs taken) and RT-prolongation, indicating IED-induced effects for prolonging RT (eReference[24], see also introduction of main manuscript). We newly performed an ANCOVA with the dependent variable RT-

prolongation and the covariates age, sex, number of ASMs taken, and session RTnormal EEG. The nominal variable of interest was the session IED type (dummy coded for focal IED, generalized atypical IED, and generalized typical IED with 1 to 3). The null model with all covariates but without IED was rejected at significance level $p<0.0001$ compared to the model with IED and the covariates, indicating highly significant differences between IED types even if all covariates are considered.

We finally controlled for a possible inhomogeneity of diurnal testing conditions, that is mainly for the drowsiness of study participants, by performing the three test types either in the late morning or in the early afternoon (starting at 2 pm).

eTable 1. De-identified patient data. Sheet "patient information, data means": Column A, codified individuals: A & B are adolescents, E are adults from 2015-2018; Epi11 are adults from the study in reference [23] and Epi16 are adults from the study in reference [24]; column B, epilepsy type/syndrome: CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonus epilepsy; GGE, genetic generalized epilepsy; IGE with GTCS, idiopathic generalized epilepsy with tonic-clonic seizures; FLE, frontal lobe epilepsy; TLE, temporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; sE, structural epilepsy; FCD, focal cortical dysplasia; AVM, aterio-venous malformation; SAH, subarachnoidal hemorrhage; SPMS, secondary progressive Multiple Sclerosis; TBI, traumatic brain injury; E-uO, epilepsy of unknown origin; DDx, differential diagnosis; column C, antiseizure medication (dose in mg/kg/day taken at the time of the test sessions): LEV, levetiracetam; ZNS, zonisamide; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; ETX, ethosuximide; PER, perampanel; PRM, primidone; TPM, topiramate; VPA, valproic acid; GBP, gabapentin; PB, phenobarbital; BBX, barbexaclone; CLZ, clonazepam, CLB, clobazam; column D, age, sex; column E, type of test session with its duration in minutes; column F, most frequent IED type in respective test session; column G, No of stimuli during normal EEG; column H, session mean reaction time (RT) during normal EEG; column I, No of stimuli during all IEDs (with miss/crash and without miss/crash); column J, session mean RT during IEDs; column K, session mean RT-prolongation by IEDs without miss/crash; column L, session mean duration of IEDs without miss/crash; column M, session mean trigger latencies of IEDs without miss/crash; column N, No of missed reactions/crashes during normal EEG; column O, miss/crash probability$_{\text{normal EEG}}$ for the respective session; column P, No of missed reactions/crashes during IEDs; column Q, session miss/crash probability$_{\text{IED}}$; column R, session mean duration of IEDs with miss/crash; column S,

session mean trigger latencies of IEDs with miss/crash; column T, mean peak frequency of IED per test session. Mean values with standard deviation are given as mean (SD). "(-)" indicates that standard deviation (SD) could not be calculated because there was only one IED in the session, or that the EEG could not be revisited at a later timepoint to determine the SD.

eTable 2. Presents recorded and calculated parameters as medians with 95%-confidence intervals (95%-CI).

eTable 3. Gives 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.

eFigure 1. Examples of the three IED types analyzed in this study. A) shows a focal IED-burst, taken from an EEG recording of an adolescent who drove in the simulator. That is, the EEG was recorded in an eyes-open condition and in ten channel reference montage. We had to reduce the number of recorded channels only in the simulator, because of our custom-made iRT device that we used to automatically detect IEDs and trigger a stimulus, record braking and RTs, and display the EEG (eMethods). **B)** shows a generalized atypical IED, taken from an EEG of an adult who drove in the simulator. **C)** shows a generalized typical IED, taken from an EEG of an adult who performed the car test. Here as well, the EEG was recorded in the eyes-open condition and in longitudinal bipolar montage.

eFigure 2. Total stopping distance, reaction distance, and braking distance in the simulator. A) All measured speeds (speed) and total stopping distances (brake) at normal EEG and IED (one point corresponds to one single measurement). Calculated total stopping distances using fixed initial speed as a function of RT. All data are described per group with the median

and 95%-CI (in red, medians written above scatter plots). **B)** Total stopping distance is composed of braking distance, which mainly depends on vehicle factors, and the reaction distance, which is the distance travelled until the driver realizes to brake. Measured braking distances averaged at session level and shown as bivariate data during normal EEG and IED were grouped by age (green, adolescents; blue, adults). Each point corresponds to one subject and one session. The line of identity indicates equal values on the x-axis and y-axis. **C)** Measured reaction distances, shown as bivariate values during normal EEG and IED in a scatter plot, were grouped by age. Each point corresponds to one subject, shown separately for adolescents (green) and adults (blue) A permutation test was performed to investigate differences in bivariate distributions between age groups. **D)** Measured speed averaged at the session level and shown as bivariate values during normal EEG and IED were grouped by age (green, adolescents; blue, adults). The identity line indicates equal values on the x-axis and y-axis. **E)** Reaction distances calculated for an initial speed of 100 km/h at stimulus presentation, averaged at the session level for periods with normal EEG (on the x-axis) and for IEDs (on the y-axis), and grouped by age (green, adolescents; blue, adults). A permutation test was performed to investigate differences in bivariate distributions between age groups.

eFigure 3. The temporal coincidence of the test task and IED is important for the magnitude of both RT-prolongation and miss/crash probability.

A) The measured time of visual stimulus appearance relative to the onset of IEDs without miss/crash was calculated as the average trigger latency of each session (one point corresponds to one session) grouped by test type and described with the median with 95%-CI (in red, medians written above scatter plots). **B)** Normalized trigger latency is the division of the average trigger latency by the average duration of IEDs without miss/crash at the session level (one dot equals

one session). Normalized session trigger latency was grouped by test type and described with the median and 95%-CI. **C)** RT-prolongations due to single IED-bursts without miss/crash from 148 sessions were calculated for each tenth of a normalized IED (defined as normalized trigger latency of zero corresponding to IED onset and a latency of one corresponding to IED end). To show the distribution of RT-prolongation over the course of an IED, a normalized IED was divided into 10 tenths, and all RT-prolongations with a normalized triggering latency within a specified tenth were averaged and presented as median with 95%-CI. **D)** The measured time of visual stimulus appearance relative to the onset of IEDs with miss/crash was calculated as the average trigger latency of each session (one point corresponds to one session) grouped by test type and described with the median and 95%-CI. **E)** Normalized trigger latency is the division of the average trigger latency by the average duration of IEDs with miss/crash at the session level (one dot equals one session). Normalized session trigger latency was grouped by test type and described with the median and 95%-CI. **F)** The miss/crash probability for a single IED-burst from the 34 sessions with ≥ 1 miss/crash was calculated for each tenth of a normalized IED by calculating the miss/crash probability for IEDs with normalized triggering latencies in a specific tenth. All IEDs with, for example, normalized triggering latencies >0.2-0.3 were used to calculate the number of misses/crashes divided by the total number of stimulus exposures during the IED for that third tenth.

eFigure 4. Distributions of RT-prolongation and miss/crash probability over the duration of normalized IEDs, separately for each IED type.

Split of data from eFigure 3C into the distributions of RT-prolongations by single focal IEDs **(A)**, single generalized atypical IEDs **(B)**, and single generalized typical IEDs **(C)** over the duration of a normalized IED. For (A)-(C), medians are shown with 95%-CI for each tenth of a

normalized IED. Accordingly, the data from eFigure 3F are also split into the distributions of single IED miss/crash probabilities for sessions with predominant focal IEDs **(D)**, generalized atypical IEDs **(E)**, and generalized typical IEDs **(F)** over the duration of a normalized IED.

eFigure 5. Distributions of RT-prolongation and miss/crash probability over the duration of normalized IEDs, separately for each test type.

Split of data from eFigure 3C into the distributions of single IED RT-prolongations in the flash test **(A)**, car test **(B)**, and simulator **(C)** over the duration of a normalized IED. For (A)-(C), medians are shown with 95%-CI for each tenth of a normalized IED. Accordingly, the data from eFigure 3F are also split into the distributions of single IED miss/crash probabilities for sessions performed with the flash test **(D)**, car test **(E)**, and simulator **(F)** over the duration of a normalized IED.

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