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Review

Driving status of patients with generalized spike–wave on EEG but no clinical seizures

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ABSTRACT

Generalized spike–wave discharges (SWDs) are the hallmark of generalized epilepsy on the electroencephalogram (EEG). In clinically obvious cases, generalized SWDs produce myoclonic, atonic/tonic, or absence seizures with brief episodes of staring and behavioral unresponsiveness. However, some generalized SWDs have no obvious behavioral effects. A serious challenge arises when patients with no clinical seizures request driving privileges and licensure, yet their EEG shows generalized SWD. Specialized behavioral testing has demonstrated prolonged reaction times or missed responses during SWD, which may present a driving hazard even when patients or family members do not notice any deficits. On the other hand, some SWDs are truly asymptomatic in which case driving privileges should not be restricted. Clinicians often decide on driving privileges based on SWD duration or other EEG features. However, there are currently no empirically-validated guidelines for distinguishing generalized SWDs that are "safe" versus "unsafe" for driving. Here, we review the clinical presentation of generalized SWD and recent work investigating mechanisms of behavioral impairment during SWD with implications for driving safety. As a future approach, computational analysis of large sets of EEG data during simulated driving utilizing machine learning could lead to powerful methods to classify generalized SWD as safe vs. unsafe. This may ultimately provide more objective EEG criteria to guide decisions on driving safety in people with epilepsy.

1. Introduction

On the electroencephalogram (EEG), generalized seizures and epilepsies are characterized by generalized spike–wave discharges (SWDs). These epileptiform discharges are most common in childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME). However, varieties of generalized SWDs may be present in other disorders (such as metabolic encephalopathies) or even as benign EEG variants (as in 6 Hz "phantom" spike–wave) [1,2]. Mechanistically, SWDs are thought to share a similar involvement of thalamocortical networks, but the EEG features (i.e., amplitude, frequency, and, rhythmicity) of the discharges and the accompanying clinical features differ among seizure and epilepsy types. Emerging evidence from hemodynamic, electrophysiology, and behavior studies suggest that EEG features of the discharges may predict the extent of behavioral impairment, indicating a possibility of using EEG characteristics to predict driving safety of patients with epilepsy, particularly those with subclinical SWDs.

2. Natural history and clinical course of generalized spike–wave epilepsy

The four classic generalized epilepsy syndromes consist of CAE, juvenile absence epilepsy (JAE), JME, and generalized tonic–clonic alone (GTCA) [3,4]. These epilepsies are similar in their suggested genetic etiologies, nonfocal onsets, involvement of thalamocortical networks, and characteristic generalized SWDs on EEG that can be provoked by sleep deprivation, hyperventilation, and photic stimulation. With frontally predominant 2.5–4-Hz generalized SWDs over normal EEG background, absence seizures are observed in CAE and JAE and are often associated with brief (3–10 s) lapses in consciousness with cessation of ongoing

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activity followed by a rather immediate return to activity [5,6]. Juvenile myoclonic epilepsy typically presents in adolescence with myoclonic, tonic–clonic, and absence seizures exhibiting frontally predominant 3.5–5-Hz polyspike–wave discharges on EEG. Ten to 37% of patients with JME have absence seizures, and subclinical epileptiform discharges may persist and confer cognitive impairments [7–9]. Generalized tonic–clonic alone typically presents in late adolescence with generalized tonic–clonic seizures (GTCs); absence seizures are uncommon manifestations. Cessation of activity in absence seizures and GTCs poses an obvious risk to complex behaviors such as driving. The generalized epilepsies are more thoroughly reviewed elsewhere [10,11].

Generalized SWDs, and for that matter, generalized seizures and epilepsies, confer variable behavioral impairments, suggesting that generalized seizures do not always involve the brain the same way [12–14]. Absence seizures commonly seen in CAE, JAE, and JME have been best studied for their varied behavioral effects among patients and among seizure episodes in the same patient. These studies, which have employed behavior testing paradigms ranging from simple repetitive tapping to responding to verbal stimuli, have identified interesting behavioral features of absence seizures. Tasks that place higher demands on decision-making and attention are more likely to identify behavioral and cognitive impairments during seizures [13,15–17]. In investigations using tasks requiring verbal responses during seizures, subjects demonstrate varied levels of impairments: while some do not respond at all, others turn their gaze to the examiner without verbally responding; still others respond appropriately [18–20]. Absence seizures are less frequent in mentally demanding tasks, and they can be ended by external stimulation [19,21,22]. Studies have reached differing conclusions on whether behavioral impairments differ between absence seizures in CAE, JAE, and JME [23–26]. The possible role of physiological properties of SWD in determining behavioral severity is discussed further in the sections that follow.

It is important to clearly define the difference between absence seizures and subclinical generalized SWD. Absence seizures are defined based on the presence of both generalized 3–4-Hz SWD and impaired behavioral responsiveness. In contrast, truly subclinical generalized SWDs produce no behavioral deficits. However, behavioral deficits in absence seizures are not always easy to detect by family members or even by basic clinical observation, making this distinction challenging in some patients. Apparently "subclinical" generalized SWDs, i.e., those that are not accompanied by obvious clinical impairments may, nevertheless, demonstrate subtle behavioral deficits that are not appreciated by the patient, relatives, or clinicians but can be demonstrated on specialized behavior testing [13,17,27–30]. Specialized testing may be needed to detect deficits either because the deficits are subtle (e.g., slowed reaction times) or because they are severe (e.g., completely missed responses) but very brief and, therefore, will be missed without critically timed and brief stimuli. Because such behavioral testing is not readily available to many clinicians, some have proposed defining absence seizures purely based on EEG duration greater than 3 or 4 s. Although it is true that longer generalized SWDs on EEG are more likely to impair behavior than shorter ones [23,31], there are many exceptions to this rule. For example, several studies have demonstrated transient impairments in cognition in generalized SWD as brief as 0.5 s long and, conversely, no impairment with generalized SWD lasting much longer than 4 s [28,30,32–35]. Therefore, absence seizures should not be defined based on EEG duration alone. Careful behavioral testing is needed to determine whether generalized SWDs cause deficits or not. Importantly, deficits in apparently subclinical SWD can include subtle changes in reaction times but can also include brief episodes of complete behavioral arrest [34,36,37]. Research on driving has demonstrated that glancing away from the road for as brief as 1 s significantly increases the risk of a crash [38,39]. Therefore, transient behavioral arrest even during a brief SWD could potentially be catastrophic if it coincides with the appearance of an obstacle while driving. Conversely, some SWD may be truly asymptomatic and should not lead to restriction of driving privileges. More research is needed to understand how to best distinguish these situations and determine driving safety in patients with generalized SWD.

Generalized seizures and epilepsies demonstrate different courses over the lifetime of patients. In one meta-analysis of 23 study cohorts representing 2303 patients with CAE, seizure remission rates ranged from 21% to 89%, reflecting heterogeneous inclusion criteria and methodologies of the different studies [40]. An estimated two-thirds of patients with CAE achieve remission of seizures later in adolescence, ceasing to need treatment indefinitely [40–43]. Yet, patients with CAE who develop GTCs in the course of their disease are less likely to achieve remission of absence seizures [40]. Unlike patients with CAE whose seizures often remit with age, patients with JAE, JME, GTCA, and other epilepsy syndromes characterized by generalized SWDs are also less likely to achieve remission of seizures without medications and typically need treatment for life [44–46]. Even in clinical remission, patients may still have apparently subclinical generalized SWDs on EEG, and, as already noted, these epileptiform discharges may be associated with neurocognitive and/or behavioral impairments detectable only with specialized testing [17,27–30]. Because the true behavioral significance of apparently asymptomatic generalized SWD is often uncertain in standard clinical practice, clinicians are presented with a challenging dilemma when asked about driving privileges.

3. Driving safety and epilepsy

Given its obvious relation to employment and access to social, educational, and economic opportunities, it is no surprise that in one survey of 81 patients with epilepsy, driving was the most frequently cited area of concern [47]. Although patients highly value their driving privileges, most nations (and states, in the U.S.) have regulations restricting these privileges. For lawmakers, the challenge is in establishing restrictions that suitably balance patients' driving privileges and safety as well as the public's safety. This challenge is reflected in the varied and often-changing driving regulations. For example, in the United States, individual states maintain the right to enact laws restricting driving among people with epilepsy. While most states require seizure-free intervals of 3 months or longer (median of 6 months), some states adopt evaluations by physicians and/or medical advisory boards, giving room for consideration of factors such as changes in antiepileptic drugs, presence of auras, or nocturnal seizures [48,49]. In the United States, 6 states – California, Oregon, Nevada, Delaware, Pennsylvania, and New Jersey – mandate healthcare providers to report seizures to driver licensing authorities. In general, countries in the European Union require 1 year of seizure freedom before granting driving privileges, but there are allowances for patients with nocturnal seizures only, seizures that never impair consciousness, etc. [50,51]. The Epilepsy Foundation of America maintains a database for up-to-date driving laws in the various US states. Similarly, the UK Epilepsy Society maintains an online interactive guide on driving privileges of people with epilepsy [52].

Variations in regulations on driving privileges of people with epilepsy are very much a reflection of our limited knowledge of risk of motor vehicle crashes (MVCs) among people with epilepsy. Most studies attempting to quantify MVC rates among people with epilepsy have relied on surveys and retrospective reviews of medical and government databases. These studies have largely suggested a moderate increase in MVC rates among people with epilepsy, but there are a few studies that have found no increase in MVC rate among people with epilepsy [53]. One study reviewing Wisconsin transportation records and medical records of people with epilepsy from one medical center (241 people with epilepsy and 30,420 controls) estimated the relative risk of a MVC at 1.33 (p-value = 0.04), suggesting a slightly increased risk of MVCs among people with epilepsy [54]. In a more recent study that surveyed 16,958 people with epilepsy and 8888 controls, the investigators found no increase in the risk of MVCs among people with epilepsy (odd ratio, OR = 0.77) after adjusting for driving experience, mileage, age, and sex [55]. However, that same study found a 40% increase in risk for serious injuries from MVCs among

people with epilepsy. In the US, an estimated 0.2% of annual fatalities from MVCs are attributed to seizures, but there is some evidence that seizure-related MVCs are more likely to result in severe injuries and/or property damage when compared with MVCs not related to seizures [55–57].

More complex than defining the MVC rate among people with epilepsy is determining the appropriate length of seizure freedom before granting driving privileges. In an earlier study, seizure freedom of more than 3 years significantly reduced the risks of having any MVC (OR: 0.74, 95% CI: 0.62, 0.87) and MVCs that result in injuries (OR: 0.66, 95% CI: 0.46, 0.93) [55]. Subsequent studies have shown an association between longer seizure-free intervals and significantly reduced MVC rates [58,59]. In the 2005 European Union's regulations, 20% seizure recurrence rate was adopted as the tolerable Chance of an Occurrence of Seizure in the next Year (COSY) among noncommercial drivers. Using data from more than 630 subjects in the Multicentre study of early Epilepsy and Single Seizures (MESS), Bonnett et al. showed that at six months after an unprovoked index seizure, the risk of seizure recurrence in the subsequent 12 months was less than 20% for those who started antiepileptic drugs [59]. The risk for those who did not start Antiepileptic Drugs (AEDs) was 18%. Similar findings have been reported using data from the UK-based multicenter Standard versus New Antiepileptic Drugs (SANAD) study [60].

The current evidence on auras in reducing risk of MVCs among people with epilepsy is inconclusive. Some previous studies had suggested that people with seizures that are preceded by auras were less likely to have MVCs, but findings in more recent studies have differed [55,61–63]. In a recent study of 215 patients reporting seizures that occurred while driving, 40.4% of patients with history of seizure-related MVCs reported having reliable auras; this was similar (p-value = 0.56) to the 44.6% of those without histories of seizure-related MVCs who reported having reliable auras.

Seizure semiology such as hallucination, visual or motor impairment, and loss of consciousness may be related to risk of MVCs [64]. In a limited study recording 22 seizures in 13 patients playing a computerized driving game, *rFactor*, driving impairment during seizures was highly variable, showing severe impairment in some seizures and no impairment in others [65]. Differences in the reported rates of MVCs among people with epilepsy clearly demonstrate the limitations of retrospective methods employed in previous studies. Well-designed prospective studies are needed to establish the risk of MVCs and to conclusively identify associations between seizure-related features and MVC rates [66].

In addition to deficits during seizures, other relevant factors for driving safety in patients with epilepsy may include patient age, effect of antiepileptic medications, and other epilepsy comorbidities including structural and connectivity abnormalities and cognitive impairments associated with the underlying disorder [67–73]. In JME, for instance, there is evidence of impaired working memory and increased risk-taking behavior, and ethosuximide, the most commonly used medication in treating absence epilepsy, may result in psychomotor slowing and attentional dysfunction.

The possible role of apparently subclinical or interictal epileptiform discharges in epilepsy driving safety is also important to consider. Effects of focal interictal spikes on cognition are discussed extensively elsewhere, and here, we instead focus on apparently subclinical generalized SWD. Given the previously discussed influence of generalized SWDs on simple behavioral tests like repetitive tapping, it is necessary to investigate the influence of generalized SWDs on driving, a more complex behavior. Generalized SWD even as brief as 1 s or less can interfere with behavior, including episodes of complete behavioral arrest [34,36,37]. Given that distractions or glancing away from the road for as brief as 1 s can significantly increase crash risk while driving, this is an important clinical problem. Aldenkamp and Arends have pointed out that the acute behavioral effects of subclinical epileptiform discharges may be overestimated and that deficits may instead be due to chronic interictal attentional impairment, or subtle seizures misidentified as interictal discharges [71]. Nevertheless, although most clinicians will allow patients with brief focal interictal epileptiform discharges to drive, in the case of frequent brief generalized SWD, many clinicians are reluctant to let patients drive without direct evidence that their ability to respond is intact. Such evidence is challenging to obtain in a clinical setting, and no current widely accepted standards exist for evaluating driving safety in patients with subclinical generalized SWD. Limited studies of driving during epileptiform activity, including generalized SWD, have provided some initial evidence of impaired driving in some cases including virtual crashes [28,65,74–76]. Therefore, more prospective research is needed to fully investigate behavioral impairment specifically during generalized SWD and to determine the mechanisms and electrographic characteristics of SWD that do or do not present a safety hazard. In the sections that follows, we first discuss recent work elucidating possible mechanisms of impaired consciousness in generalized SWD and next, return to applications to driving safety.

4. Mechanisms of behavior impairment in generalized SWDs

In earlier works employing EEG and video recordings while subjects completed cognitive and Intelligence Quotient (IQ) tests, Aldenkamp and colleagues demonstrated that occurrence of generalized epileptiform discharges – even when subclinical – resulted in transient impairments in cognitive function that potentially accumulated over time and partly accounted for long-term cognitive and intelligence deficits in some epilepsy syndromes [77–79]. Presumably, transient cognitive impairments such as prolongation of reaction time during subclinical generalized epileptiform discharges affect more than performance on neuropsychological testing and may even affect driving as more recent studies have demonstrated [74,75]. Recent advancements in EEG analysis and functional neuroimaging have provided opportunities to investigate associations between features of generalized SWDs and behavioral impairments. While there remains much work to be done in this area, findings from the few available studies have advanced our understanding of the mechanisms underlying behavioral deficits observed in generalized SWDs, and we are gaining grounds in predicting the influence of SWDs on behavior.

It has long been recognized that alterations in consciousness vary at different times during a given episode of SWD. Earlier studies using motor and verbal tests reported only subtle behavioral impairments in the first 3 s and the last 3–5 s of absence seizures; more severe impairments occurred in the intervening seconds of the discharges [15,80,81]. Later studies employing reaction time studies demonstrated that impairments are detectable at onset of SWDs or even in the preceding seconds [15,82]. Further, there is evidence from tapping tasks that behavioral deficits in generalized SWDs may persist for a few seconds after cessation of the epileptiform discharge [15,20]. The differing results of these studies are reflective of the different behavioral tests employed, suggesting that the severity of behavioral and cognitive impairments during generalized SWDs may be associated with specific tasks and time courses during the seizures.

More recent studies using the blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) have replicated and extended some of the findings of these earlier studies. Bai et al. recorded EEG and fMRI during 88 typical absence seizures in 9 children while completing continuous performance tasks (CPTs) and repetitive tapping tasks (RTT) [83]. Significant impairments in performance on both behavior tests were noticed during SWDs but were more severe on the more attentionally demanding CPT compared with the easier RTT task. In addition, behavior tended to gradually improve towards the end of SWD for both tasks. Concurrent BOLD-fMRI showed signal increases in orbital/medial frontal and medial/lateral parietal cortex more than 5 s before onset of electrographic seizures; signal decreases were noticed to last more than 20 s after seizure end. Another recent study of children with CAE showed variable behavioral impairment associated with variable fMRI amplitude from one SWD to the next even in the same patient [34]. Of note, behavioral impairment in some cases included complete behavioral arrest in response to external stimuli during SWD

lasting as briefly as 2 s whereas other SWD lasting as long as 8 s caused no behavioral impairment [34]. In an interesting single case report, Moeller et al. reported the absence of any cognitive impairment in a 14-year-old girl who had generalized SWDs lasting up to 10 s during EEG-fMRI recording with CPT [84]. Again, generalized SWDs demonstrate dynamic behavioral influences based on the difficulty of the task, the involved cognitive domains, and the specific time during the course of the discharge. This dynamism of SWDs suggests involvement of different subcortical–cortical networks or involvement of networks to varying degree, in generation, maintenance, propagation, and termination of these seizures.

Given the variable impact of generalized SWDs on behavior and cognition, some investigators have explored the associations between clinical features (like age and epilepsy syndrome) and EEG features of the SWDs. Moreover, others have explored associations between EEG features of SWDs and behavioral impairments. Reviewing 509 seizures in 70 children with CAE, JAE, or JME, Sadleir et al. observed that the specific epilepsy syndrome was associated with the number of spikes per wave in a given seizure, with JME and JAE having similar number of spikes per wave but more than CAE [85]. In the same study, older subjects were more likely to have organized SWDs, and neither seizure duration (p-value = 0.66) nor presence of clinical features (p-value = 0.14) was associated with the number of spikes per wave. Seizures provoked by photic stimulation were at increased likelihood to have polyspikes on EEG than did seizures provoked by hyperventilation. These results demonstrate the intricate relationship between clinical features and EEG features of generalized SWDs.

Earlier behavioral tests suggested that longer seizures, larger amplitude, or other EEG features lead to more severe impairments in behavior, although differing results have been reported by some studies [15,17,23,35,86–91]. In one study reviewing video-EEG recordings of 509 absence seizures in 70 treatment-naive children with diagnosis of CAE, JAE, or JME, patient's age and seizure duration significantly influenced the level of awareness during seizures [23]. Older children were more likely to be aware during seizures, and children were more likely to be aware during briefer seizures.

Recent work combining EEG and fMRI in absence seizures demonstrates that both the duration and the physiological amplitude of generalized SWDs are associated with the extent of behavioral impairment during the discharges. Guo and colleagues recorded EEG-fMRI of seizures in 39 children who also completed behavioral testing with CPT and RTT [31]. As had been previously shown, performance on both CPT and RTT markedly declined during SWDs. Of more interest, SWDs during which subjects performed more poorly on behavior tests lasted longer (7.9 s vs. 3.8 s; p-value < 0.0001) and were associated with larger amplitudes of EEG and fMRI signals in widespread regions of the brain (Figs. 1, 2, and 3). The larger EEG and fMRI signal amplitudes in the behavior-impairing SWDs were observable in the seconds preceding seizure onset and in three established neural networks (i.e., default-mode, task-positive, and primary sensorimotor-thalamic networks) (Fig. 3).

The involvement of generalized SWDs with established networks necessary for attention and information processing has been demonstrated in other EEG-fMRI studies, shedding light on the subcortical–cortical networks involved in these epileptiform discharges [34,92–105]. Together, these findings suggest that generalized SWDs that impair consciousness and behavior take advantage of preceding vulnerable states, recruit more neurons, and induce intense physiologic changes in established neural networks resulting in widespread cortical and subcortical

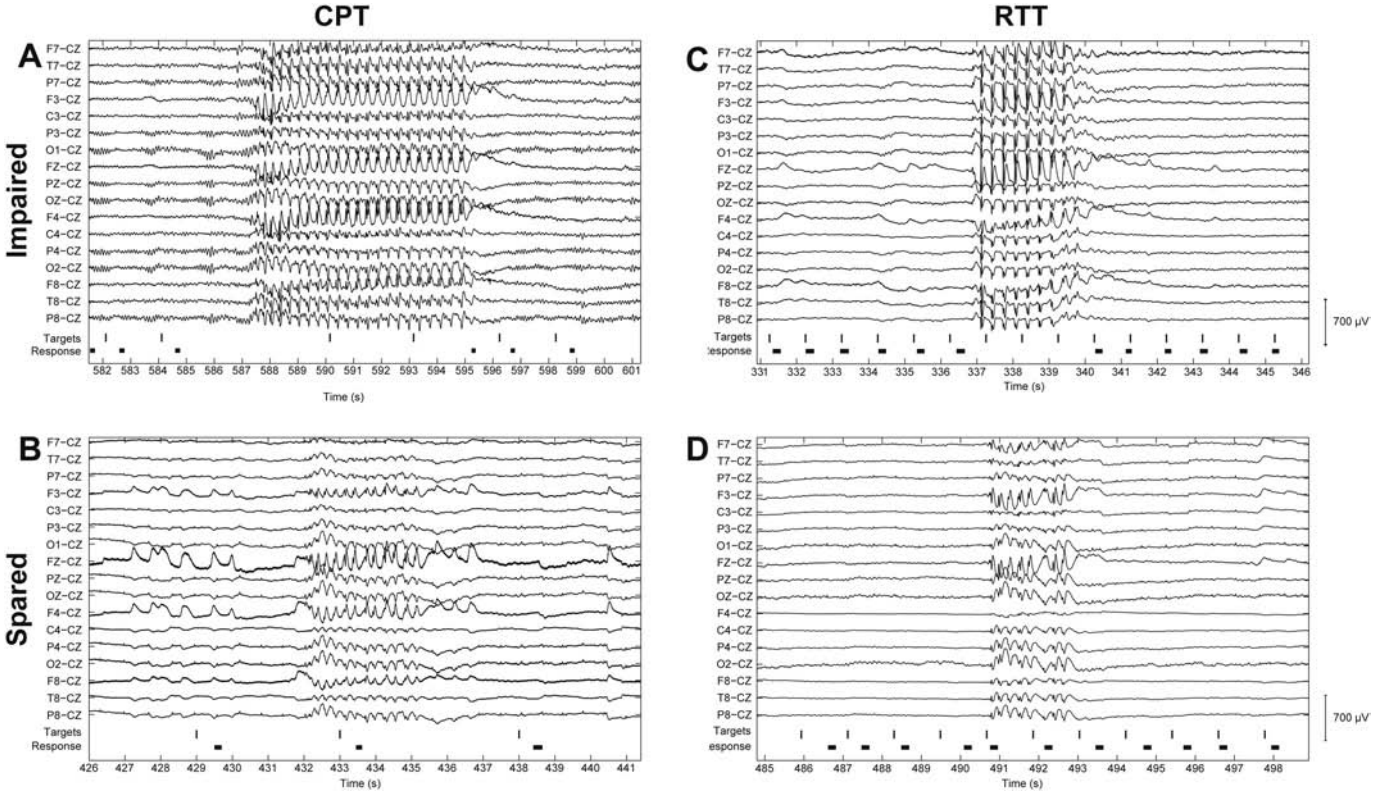

Fig. 1. Examples of EEG recordings showing generalized spike–wave discharges with impaired versus spared performance. On both the continuous performance task (CPT, A and B) and repetitive tapping task (RTT, C and D), generalized SWDs that resulted in impaired performance (A and C) lasted longer than those that spared performance (B and D). Shown here are out-of-scanner high-density EEG recordings with a limited number of channels shown for ease of viewing. Vertical lines indicate presentation of target letters during behavioral tasks. For CPT (A and B), the targets consisted of the letter "X" presented in a stream of other letters appearing once each second. For RTT (C and D), the targets consisted of any letter presented once each second. Durations of button presses are indicated by the heavy black horizontal lines.
Reproduced with permission from Guo et al., Impaired consciousness in patients with absence seizures investigated by functional MRI, EEG, and behavioural measures: a cross-sectional study. *Lancet Neurology*, 2016; 15(13) 1336–1345.

involvement. While fMRI offers valuable insights into SWD pathophysiology, EEG remains a more clinically accessible tool for widespread use. Therefore, further investigation of EEG features which may predict altered responsiveness and impaired driving safety with SWD will be crucial in order to provide clinically useful guidance to patients and their healthcare providers regarding driving safety.

5. Driving evaluation in generalized SWDs

In some jurisdictions like Australia and Britain, an individual who continues to have epileptiform discharges on EEG may be denied driving privileges even after satisfying the required seizure freedom period [106,107]. This raises questions on the utility of the EEG and its predictive value in evaluating driving safety among people with epilepsy. Studies attempting to answer these questions are few, but their results have been informative.

Prolonged EEG evaluation is preferable to routine ambulatory EEG in defining seizure freedom and predicting seizure relapse among people with epilepsy. One study retrospectively analyzed reports from routine EEG and 6-hour video-EEG monitoring of 34 patients, 26 (76%) of whom had genetic generalized epilepsy [108]. Twenty-seven of the 34 patients were assessed as fit to drive based on interpretation of video-EEG by treating neurologists. Within 2 years of follow-up, 5 (19%) of the 27 deemed fit to drive had seizure relapses, albeit with identifiable precipitating factors. All 7 patients who had been assessed unfit to drive had seizure relapses (unprovoked in 4 patients) in the follow-up period. Thus, the relative risk of seizure relapse following an assessment of being unfit to drive based on 6-hour video-EEG monitoring (VEM) was 5.4 (p-value = 0.00015). The relative risk among patients with genetic generalized epilepsy was 4.0 (p-value = 0.002). Interestingly, using the routine 30-minute EEG reports alone, the relative risk of seizure relapse after being assessed fit to drive was 3.4 (p-value = 0.037) [108].

Prolonged EEG monitoring may be invaluable in identifying epileptiform activities that would otherwise be missed on routine EEG or are not reported by the patient and/or relatives during evaluation for granting driving privileges to people with epilepsy. A retrospective study analyzing 24-hour ambulatory EEGs of 1100 patients identified 57 patients, 15 of whom had genetic generalized epilepsy, with ictal events on EEG that were not reported by the patients and their relatives [109]. Of the 57, 21 patients had been assessed as seizure-free, and at least 18 of them were driving regularly. Patients and their relatives may fail to recognize and report some manifestations of seizures because of limited knowledge of their diseases [110], postictal amnesia, or even in attempt to avoid driving restrictions. In such cases, prolonged EEG monitoring can help direct decision-making by physicians, medical advisory boards, and driver licensing authorities during assessments for granting or renewing driving privileges.

Despite the utility of prolonged EEG, without concurrent behavioral testing, the true risk of generalized SWD without obvious behavioral manifestations remains unknown. Conceivably, the gold standard for evaluating driving in people with epilepsy would be a realistic, EEG-monitored driving experience on a road for a sufficient length of time. Such test poses several concerns with regard to safety and defining the appropriate length of recording time and parameters for assessing driving safety, but this effort has been attempted. Trenité and colleagues recruited six patients with spontaneous subclinical epileptiform discharges to drive in a car equipped to record EEG and monitor driving parameters like positioning, speed, and steering [29]. The subjects drove for 420 km (i.e., 3 runs of 140 km each) on a motorway. All 4 subjects who had been seizure-free for 4 or more years had subclinical generalized (poly) spike–wave discharges on EEG during the test sessions. In 3 subjects (2

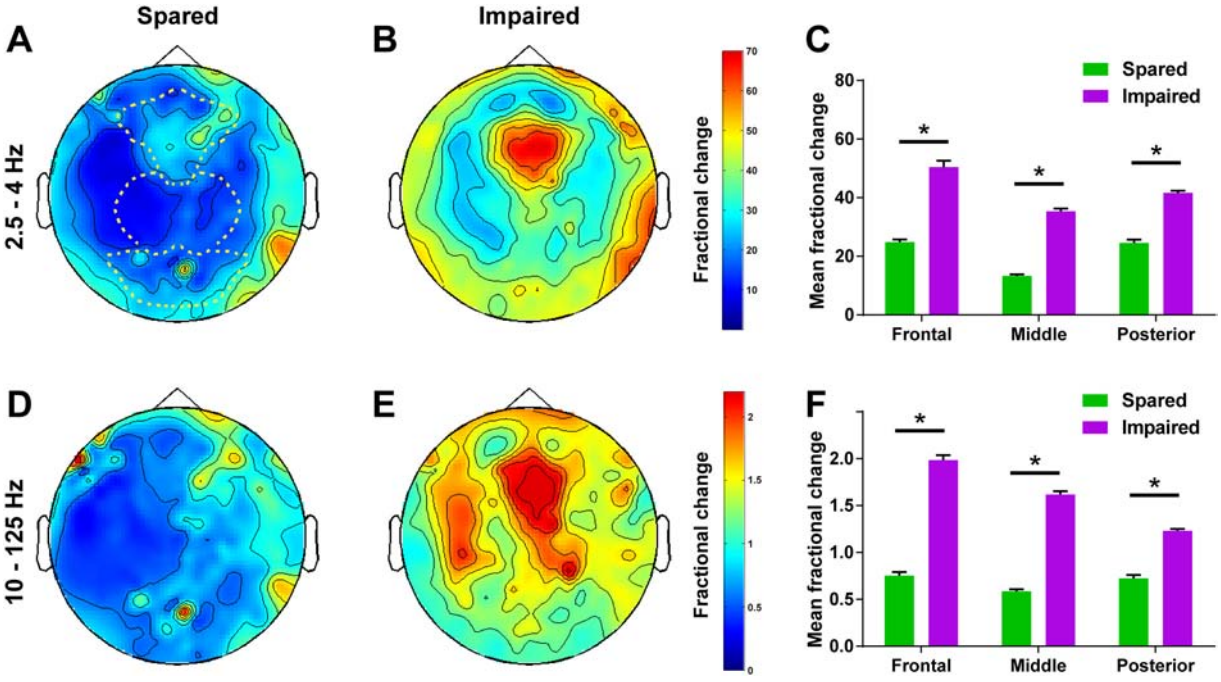

Fig. 2. Generalized SWDs with impaired performance on CPT and RTT are associated with greater EEG amplitude in widespread brain regions. (A and B) Wave component of SWDs represented by head maps of 256-channel high-density EEG power in the 2.5–4-Hz frequency range for both performance-sparing (A) and performance-impairing (B) SWDs. (C) Mean fractional EEG power in the 2.5–4-Hz frequency range for seizures with spared versus impaired performance. (D and E) Spike component of SWDs represented by head maps of EEG power in the 10–125-Hz frequency range for both spared (D) or impaired (E) performance. (F) Mean fractional EEG power in the 10–125-Hz frequency range for seizures with spared versus impaired performance. Color scale bars are EEG power during seizures divided by baseline power before seizures (fractional power). The top color bar is for panels (A) and (B), and the bottom bar is for (D) and (E). Dashed lines in (A) show regions used for analysis in (C) and (F) (frontal, middle, and posterior EEG contacts). *$p < 0.0001$. Error bars represent standard error. Analysis is based on data from 30 performance-sparing seizures in 5 patients and 26 performance-impairing seizures in 8 patients.
Reproduced with permission from Guo et al., Impaired consciousness in patients with absence seizures investigated by functional MRI, EEG, and behavioural measures: a cross-sectional study. *Lancet Neurology*, 2016; 15(13) 1336–1345.

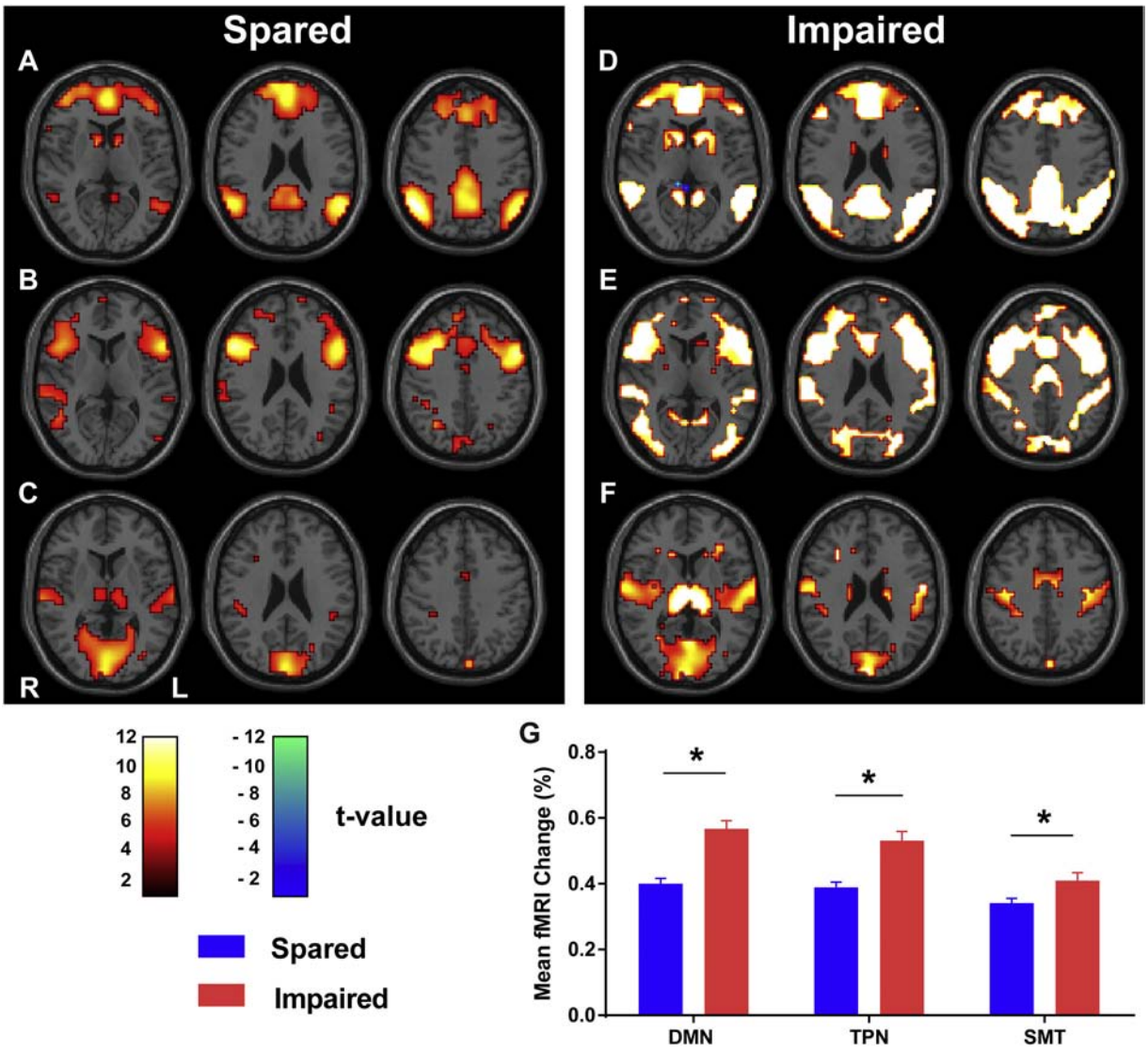

Fig. 3. Functional magnetic resonance imaging signals in three established brain networks during generalized spike–wave seizures that spared or impaired performance on behavior tests. (A, B, and C) Axial brain t-maps with fMRI signals for generalized SWDs with spared performance in the default-mode network (DMN) (A), task-positive network (TPN) (B), and primary sensorimotor-thalamic network (SMT) (C). (D, E, and F) Corresponding axial brain t-maps with fMRI signals for generalized SWDs with impaired performance. Color scale bars show t values. Hot colors (white-orange) indicate significant fMRI changes in the same direction as the network-specific hemodynamic response functions. Cool colors (green-blue) indicate changes in the opposite direction. (G) Mean percentage change in BOLD-fMRI signal across seizures in each network. Analysis is based on data from 93 performance-sparing seizures in 17 patients and 112 performance-impairing seizures in 22 patients.
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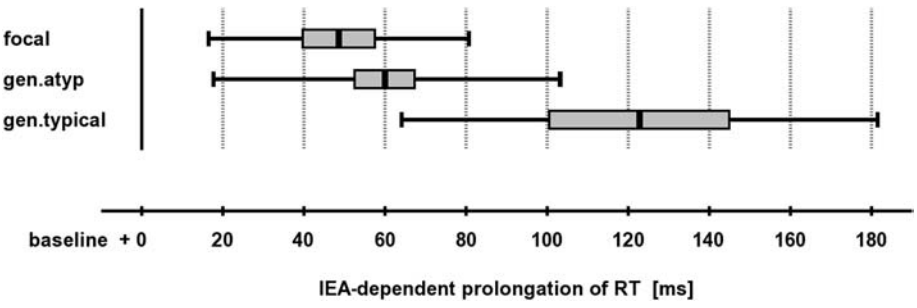

Fig. 4. Typical generalized spike–wave discharges prolong reaction time more than focal and atypical generalized spike–wave discharges on a computerized driving game. Reaction times during interictal epileptiform activity (IEA) including focal, atypical, and typical generalized spike–wave discharges are shown. Interictal epileptiform activity resulting in lapses or crashes during testing are excluded in calculating the depicted reaction times. Center value = mean, colored box = standard error of the mean, range bar = standard deviation.
Reproduced with permission from Nirkko et al., Virtual car accidents of epilepsy patients, interictal epileptic activity, and medication. *Epilepsia*, 2016, 57(5) 832–840.

with generalized SWDs and 1 with sharp waves), the epileptiform discharges were associated with significant deviations in car positioning, demonstrating impaired driving during the discharges.

Simulated driving experiences have similarly demonstrated impaired driving behavior in the interictal period and during epileptiform discharges, particularly generalized SWDs. As aforementioned, using the *rFactor* computerized game, our group has shown a likely association between seizure type and collisions [65]. Researchers in Switzerland have developed another computerized driving game, *Steer Clear*, with which they have studied the effect of interictal epileptiform activity (IEA) on driving [74,75]. In this game, an obstacle is manually introduced in the driving course during the discharges. In one study involving 46 adults (34 of whom had generalized IEA), both focal and generalized EEG discharges resulted in significant prolongation of reaction time (Fig. 4) [75]. On average, focal and atypical generalized IEA resulted in 49 ± 32-millisecond (ms) and 60 ± 42-ms prolongation in reaction time, respectively. Typical generalized IEA showed the most profound prolongation in reaction time (123 ± 59 ms) on this test in which ≥100-ms prolongation in reaction time corresponds to ≥2.8 m increase in braking distance in a car traveling at 100 km/h (approx. 62 mph). Further, the probability of virtual accidents per obstacle presentation was markedly increased during typical generalized IEA (32.0%) compared with during focal (3.5%) and atypical generalized IEA (4.1%). Like prolonged EEG monitoring, simulated driving carries great promise of utility in evaluating driving safety among people with epilepsy, whether for seizure relapse or impaired reaction to road hazards. Ideally, with additional investigation of EEG features of SWD associated with impaired driving ability, it may be possible to predict driving safety based on EEG alone, with no need for driving simulation in each individual patient.

6. Conclusion and future directions

Although previous studies have elucidated the clinical course, EEG and fMRI pathophysiology of seizures and epilepsies characterized by generalized SWDs, driving safety remains an open question for patients with SWD on EEG but no clinically obvious seizures. Many clinicians currently will use basic EEG characteristics such as SWD duration, frequency of SWD occurrence in prolonged recordings, and whether the SWD only occur during sleep, as common-sense criteria to decide on driving privileges for people with epilepsy. However, clinical practice varies widely in this regard, and there are no accepted evidence-based criteria to decide on driving privileges in patients with generalized SWD on EEG. Initial evidence suggests that EEG features such as SWD duration and amplitude may distinguish between “safe” and “unsafe” SWD at least on a population level [31]. However, further work is needed with realistic driving testing during SWD to better characterize the EEG features of SWD that do or do not present a safety hazard. With sufficient EEG and behavioral data, it may ultimately be possible to develop a machine-learning-based classifier that could predict driving safety based on EEG recordings in individual patients. Combining simulated driving, EEG, and advanced computational analysis represents the next phase of our quest to understand the influences of epileptiform discharges on complex behaviors like driving. We hope that future work will enable more objective guidelines to be developed that will better inform clinicians and improve safe decision-making for people with epilepsy and generalized SWD who wish to drive.

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Conflicts of interest

None of the authors has any conflict of interest to disclose regarding this article.

Ethical publication statement

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

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