Autonomic manifestations of epilepsy: emerging pathways to sudden death?

Roland D. Thijs[1,2,3]✉, Philippe Ryvlin[4] and Rainer Surges[5]

Abstract | Epileptic networks are intimately connected with the autonomic nervous system, as exemplified by a plethora of ictal (during a seizure) autonomic manifestations, including epigastric sensations, palpitations, goosebumps and syncope (fainting). Ictal autonomic changes might serve as diagnostic clues, provide targets for seizure detection and help us to understand the mechanisms that underlie sudden unexpected death in epilepsy (SUDEP). Autonomic alterations are generally more prominent in focal seizures originating from the temporal lobe, demonstrating the importance of limbic structures to the autonomic nervous system, and are particularly pronounced in focal-to-bilateral and generalized tonic–clonic seizures. The presence, type and severity of autonomic features are determined by the seizure onset zone, propagation pathways, lateralization and timing of the seizures, and the presence of interictal autonomic dysfunction. Evidence is mounting that not all autonomic manifestations are linked to SUDEP. In addition, experimental and clinical data emphasize the heterogeneity of SUDEP and its infrequent overlap with sudden cardiac death. Here, we review the spectrum and diagnostic value of the mostly benign and self-limiting autonomic manifestations of epilepsy. In particular, we focus on presentations that are likely to contribute to SUDEP and discuss how wearable devices might help to prevent SUDEP.

Tonic–clonic seizures (TCSs)
Focal or generalized-onset seizures consisting of a tonic followed by a clonic phase.

[1]*Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands.*

[2]*Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands.*

[3]*NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London, UK.*

[4]*Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.*

[5]*Department of Epileptology, University Hospital Bonn, Bonn, Germany.*

✉*e-mail: rthijs@sein.nl*

https://doi.org/10.1038/s41582-021-00574-w

The intimate connection between epileptic networks and the autonomic nervous system (ANS) is illustrated by a plethora of ictal autonomic manifestations including epigastric sensations, palpitations, goosebumps and syncope[1,2]. Early case descriptions in people with epilepsy helped to uncover the hidden ties between the heart and the brain. As a prelude to the discovery of the so-called 'central autonomic network' (CAN), Russell noted over 100 years ago that seizures can not only increase but also decrease heart rate:[3] "he uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable."

The paroxysmal disruptions of normal brain activity that are seen in epilepsy provide a unique model with which to explore the brain–heart axis. Since Russell's observations, substantial progress has been made in this field: functional studies have unravelled the workings of the CAN, and autonomic concepts are beginning to be translated into clinical applications. Autonomic manifestations in people with epilepsy are also attracting interest, particularly in view of their potential to predict sudden unexpected death in epilepsy (SUDEP). Emerging experimental and clinical data have been instrumental in separating autonomic alterations that might contribute to death from benign self-limiting phenomena such as ictal syncope, and in delineating the various pathways that contribute to SUDEP. Another interesting prospect is the development of wearable technologies and algorithms that use autonomic alterations to detect and provide alerts to tonic–clonic seizures (TCSs) and other seizure types.

In this article, we review the many facets of seizure-related autonomic manifestations and their diagnostic value for delineating the seizure-onset zone, with a special focus on cardiovascular and respiratory manifestations, given their potential role in SUDEP. We summarize the key anatomical structures that regulate the CAN, critically review the spectrum of presentations that are likely to contribute to sudden death and discuss the potential of wearable devices to prevent SUDEP.

Ictal autonomic manifestations

Clinical presentations

Autonomic manifestations of seizures are extremely common and might represent the key clinical ictal manifestations in some patients. Non-motor-onset focal aware or impaired-awareness seizures can be classified as 'autonomic' if they cause gastrointestinal sensations, a sense of heat or cold, flushing, piloerection (goosebumps), palpitations, sexual arousal, respiratory changes and/or other autonomic symptoms[4]. Some sensations — in particular, a rising sensation or diffuse hot–cold

Key points

- Autonomic manifestations of seizures are frequent; they are generally more prominent in focal seizures that originate from the temporal lobe and are particularly pronounced in focal-to-bilateral and generalized tonic–clonic seizures (TCSs).
- Ictal autonomic changes might serve as diagnostic clues, provide targets for seizure detection and help us to understand the mechanisms that underlie sudden unexpected death in epilepsy (SUDEP).
- Ictal asystole is the most frequent clinically relevant seizure-related arrhythmia. The key clinical expressions include flaccid falls with injuries and other signs of syncope (for example, intense pallor, jerks, stiffening and gasping) during the course of a temporal lobe seizure.
- SUDEP contrasts with self-limiting autonomic features because it typically occurs in the aftermath of a TCS, whereas ictal apnoea and ictal asystole are associated with focal — mostly temporal lobe — seizures.
- SUDEP has a spectrum of heterogeneous causes but is predominantly attributable to TCS-triggered postictal apnoea–asystole.
- SUDEP and sudden cardiac death are partially overlapping entities, and the presence of pre-existing or acute cardiac comorbidities might help to differentiate between these two events.

sensations — can also be labelled as sensory if they occur in isolation but should be classified as autonomic if they are accompanied by other autonomic symptoms or signs[5].

Ictal autonomic manifestations tend to be underreported because they might not be recognized as seizure-related, or might be too subtle or not remembered. In a prospective survey, only 11% of documented autonomic expressions were recalled by the patient[6]. In a prospective video-electroencephalogram (EEG) study, all individuals with ictal central apnoea seemed to be unaware of their apnoea[7]. In 16% of these seizures, apnoea was the sole clinical manifestation, which emphasizes the importance of polygraphic monitoring of respiration[7].

Autonomic seizure manifestations can provide clues to the localization or lateralization of the ictal onset zone but should always be considered in the context of a complete diagnostic epilepsy evaluation (TABLE 1). Most autonomic seizures originate from the temporal lobe, highlighting the important role of the limbic system in the CAN. Each sign should be evaluated in the context of preceding autonomic manifestations. For example, asystole could be the first ictal expression, but could also follow ictal apnoea or ictal hypotension. Another important aspect to consider is the seizure type and the timing of the event. For instance, ictal asystole (IA) is predominantly seen in focal seizures of temporal lobe onset, whereas postictal asystole is strongly associated with TCSs, including both primary generalized TCSs and focal-to-bilateral TCSs[8]. The same holds true for apnoea: ictal central apnoea is strongly linked to focal temporal lobe seizures, whereas postictal central apnoea is seen only in the context of TCSs[7,9].

Cardiovascular manifestations

Ictal tachycardia. Heart rate alterations are the most studied and probably the most frequent ictal autonomic signs[10]. Prevalence estimates of ictal tachycardia range from 38% to 100% owing to varying studied populations and definitions[10]. Most of these heart rate increases do not, however, meet the most commonly applied definition for sinus tachycardia (heart rate >100 bpm)[11]. Similar heart rate increases can be seen during physiological states such as exercise, nocturnal arousals or psychogenic non-epileptic seizures, although the abruptness and the accompanying changes in heart rate variability (HRV) might help to identify seizure-related tachycardia[12,13].

The degree of autonomic change varies according to the seizure type. Ictal tachycardia seems to be more prominent in seizures originating from the temporal lobe than in seizures with extratemporal lobe onset[14], and the most marked heart rate changes have been reported in TCSs[15–17]. Depth EEG recordings in people with temporal lobe epilepsy (TLE) indicate that ictal tachycardia coincides with seizure activity in the anterior hippocampus and amygdala[18]. The extent of the heart rate increase correlates with gradual seizure spread to subregions of the ipsilateral and contralateral temporal lobes[19,20].

Heart rate changes might represent the earliest clinical indicator of seizure onset and, thus, could be of interest for seizure detection[21]. In up to 36% of seizures, the heart rate was reported to increase before seizure onset could be detected on scalp EEG, with a median lag time of 11 s (REF.[14]). However, scalp EEG cannot reliably determine the timing of seizure onset, especially if seizures originate from deep brain structures, and intracranial EEG recordings have demonstrated that seizure-related tachycardia is an ictal rather than a pre-ictal phenomenon[22].

The side of the ictal onset zone does not seem to influence the risk of ictal tachycardia[23]. However, involvement of the temporal and orbitofrontal cortex, spread of seizure activity to the contralateral hemisphere and state of alertness might define the degree of ictal tachycardia[23].

Other ictal cardiovascular manifestations lack precise prevalence figures, because blood pressure parameters are not routinely assessed during video-EEG recordings. Overall, most ictal cardiovascular signs are accompanied by a shift towards sympathetic dominance[2]. Increases in blood pressure can be seen across all focal seizure types, with the most marked increases being observed in focal-to-bilateral TCSs[24]. Peri-ictal blood pressure alterations have a similar time course to the concomitant tachycardia, suggesting modulation of arterial baroreflex control[25]. In focal-to-bilateral TCSs, the attenuated baroreflex sensitivity extends throughout the postictal period, whereas no such postictal changes have been found in focal seizures[26]. In rare cases, TCSs elicit profound postictal hypotension that can coincide with postictal generalized EEG suppression (PGES), that is, overall suppression of brain activity in the postictal period[27]. An electrical stimulation study in 12 individuals with epilepsy identified Brodmann area 25 as a potential symptomatogenic zone for peri-ictal hypotension[28].

Arrhythmias. Most forms of cardiac arrhythmias can be observed in people with epilepsy, particularly in association with seizures[29]. However, the incidence of cardiac arrhythmias and the immediate effects of these

Central apnoea
Cessation of airflow for at least 10 s with no respiratory effort.

Asystole
Cardiac standstill with no cardiac output and no ventricular depolarization lasting for at least 3 s.

Focal-to-bilateral TCSs
A seizure type with focal onset, with awareness or impaired awareness, either motor or non-motor, progressing to bilateral tonic–clonic activity.

Baroreflex
Reflex mechanism through which baroreceptors maintain blood pressure homeostasis.

QRS complexes
Combination of three marked graphical deflections seen on a typical ECG, corresponding to the contraction of the large ventricular muscles.

arrhythmias on the systemic circulation vary greatly[8,30]. Perhaps the most important types are ictal bradycardia and asystole, given their impact on systemic blood flow and associated clinical events, including traumatic falls. Bradycardia is commonly defined as slowing of the heart rate below 60 bpm. Asymptomatic bradycardia is often observed in young, healthy individuals, and in particular, in trained athletes[31]. In symptomatic bradycardia, the heart rate is usually <50 bpm (REF.[32]). In most studies, IA is considered to be a seizure-related pause of regular QRS complexes of more than 3 s (REFS[8,33]). IA is typically preceded by heart rate deceleration, which is indicative of ictal suppression of sinus node activity. In some cases, IA is accompanied by a complete block of atrioventricular conduction[8].

Ictal bradycardia has been reported to occur in up to 6.4% of focal seizures and in up to 13.6% of people with epilepsy undergoing video-EEG monitoring[29]. IA was detected in 0.32% of people with refractory focal epilepsy who were admitted for video-EEG monitoring[8]. People with epilepsy who experience IA have a 40% risk of recurrent IA[33]. IA seems to occur exclusively in focal impaired-awareness seizures and mostly in people with TLE[8,33]. The cerebral mechanisms underlying ictal bradycardia and IA are not fully understood. Seizure activity could modulate the CAN, causing increased

Table 1 | **Autonomic manifestations in focal aware and impaired-awareness seizures**

Manifestation	Localization	Lateralization	Other associated seizure types
Tachycardia[2,10]	More frequent in TLE	Not consistent	Focal-to-bilateral TCS, generalized TCS
Ictal asystole[8,85]	Predominantly TLE	Not consistent	–
Postictal asystole[8]	Not consistent	Not consistent	Focal-to-bilateral TCS[a]
Hypotension[25]	Predominantly TLE	Not consistent	Focal-to-bilateral TCS[a]
Piloerection[2,68]	Predominantly TLE	Mostly ipsilateral if unilateral	–
Hyperventilation[2]	FLE or TLE	Not consistent	–
Ictal central apnoea[7,9]	Predominantly TLE	Not consistent	–
Postictal central apnoea[176]	Not consistent	Not consistent	Focal-to-bilateral TCS, generalized TCS
Laryngospasm[2]	Mostly FLE	Not consistent	–
Postictal stertor[176,177]	Not consistent	Not consistent	Focal-to-bilateral TCS, generalized TCS
Ictal urinary urge[2]	Predominantly TLE	Mostly non-dominant lobe	–
Urinary incontinence[b,2]	Not consistent	Not consistent	Focal-to-bilateral TCS, generalized TCS
Water drinking[c,2]	Predominantly TLE	Mostly non-dominant lobe	–
Postictal nose wiping[2]	Predominantly TLE	Mostly ipsilateral if unilateral	Absence seizures
Coughing[b,2]	Mostly temporal lobe	More frequent in non-dominant lobe	–
Hypersalivation[2]	Predominantly (mesial) TLE	Not consistent	–
Spitting[2]	Predominantly TLE	Not consistent	–
Epigastric aura[2,63]	Predominantly (mesial) TLE	Not consistent	–
Vomiting[2]	Predominantly TLE (adults)	Not consistent	–
Flatulence[2]	TLE or insular lobe	Not consistent	–
Mydriasis[2]	Not consistent	Not consistent	Focal-to-bilateral TCS, generalized TCS
Sexual aura[2]	Predominantly TLE	Not consistent	–
Genital aura[2]	Predominantly FLE	Not consistent	–
Sexual automatisms[2]	Predominantly FLE	Not consistent	–
Genital automatisms[d,2]	Predominantly TLE	Ipsilateral if unilateral	Absence seizures
Flushing[2]	Not consistent	Not consistent	–
Pallor[2]	Predominantly TLE	Not consistent	–
Sweating[2]	Not consistent	Not consistent	–

[a]Mostly studied in cohorts with focal epilepsy; possibly associated with generalized TCS as well but this has not yet been studied. [b]Predominantly postictal. [c]Mostly ictal. [d]Ictal or postictal. FLE, frontal lobe epilepsy; TLE, temporal lobe epilepsy.

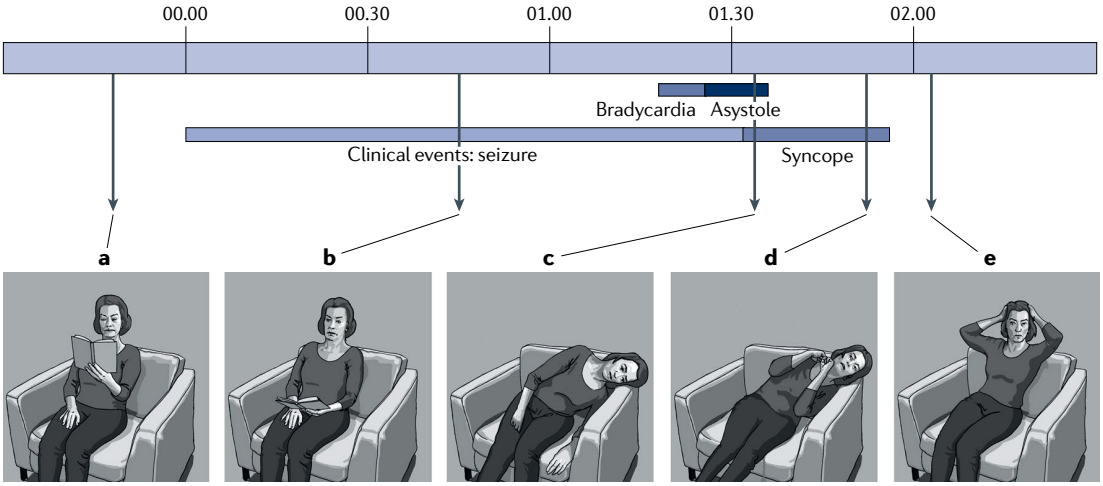

Fig. 1 | **Key semiological elements of ictal asystole.** The drawings were based on photographs of an actress imitating postures in still images of a patient video. The timeline is shown in minutes, with the start of the focal seizure as time zero. **a** | Before the seizure, the patient is reading a book. **b** | During the seizure, she stops reading, stares ahead and exhibits oral automatisms. Postural control is intact, so the trunk and head remain upright. **c** | After about 80 s, she develops bradycardia followed by 14 s of asystole. The ensuing syncope initially manifests as flaccidity. Note that her eyes are open during the seizure as well as during syncope. **d** | This stage is followed by typical syncopal motor signs, namely, flexion of the arms, extension of the legs and retroflexion of the head. **e** | When syncope ends, recovery is quick and the patient is clear-headed but amazed by the situation in which she finds herself. Parts **a**–**e** drawn by J. Gert van Dijk.

parasympathetic outflow, or indirectly provoke a vasovagal reflex. IA occurs in association with bilateral spread of seizure activity and is not specific to seizure activity in either the left or the right hemisphere[8,33–35].

Long-term ECG monitoring in patients with refractory epilepsy was found to have a low diagnostic yield of clinically relevant arrhythmias. Four studies involving a total of 280 individuals with refractory epilepsy used implanted loop recorders to ascertain the prevalence of asystole[36–39]. Monitoring of these patients for up to 3 years yielded an overall prevalence of 7%. Three of the studies, accounting for 261 patients, showed remarkably similar incidences of asystole (6%)[36,37,39]. Most of these events were short-lived and did not require pacemaker implantation. In the remaining small-scale study ($n = 19$), 21% of patients had longer-lasting asystole that required pacemaker implantation, suggesting some bias in this study population[38]. Short-duration, non-sustained ventricular tachycardia was rare, affecting only two individuals in one of the four trials[39]. The yield of long-term ECG screening might be increased by targeting special subgroups, including people with cardiac comorbidities[40] or markers of cardiac electrical instability[41,42].

Interestingly, vagus nerve stimulation seems to reduce abnormally elevated levels of T-wave alternans, thereby stabilizing the electrical properties of the heart[43]. However, whether this intervention could help to reduce the risk of sudden cardiac death due to ventricular tachycardia and ventricular fibrillation (VT/VF) is currently unknown.

T-wave alternans
Beat-to-beat fluctuations in the morphology and/or amplitude of the ST segments and/or T waves on the surface ECG.

Vasovagal syncope
Transient loss of consciousness due to global cerebral hypoperfusion evoked by a vasovagal reflex.

Syncope. Syncope is defined as transient loss of consciousness caused by global cerebral hypoperfusion[32]. In general, asystole lasting for 8 s or longer commonly leads to loss of consciousness and atonia[44], and individuals with vasovagal syncope have a 27–42% of risk of falls and injuries[45,46]. Given that the average duration of IA is 20 s, most individuals with this condition will develop symptoms and signs of cerebral anoxia[8]. IA with subsequent syncope (ictal syncope) is characterized by sudden loss of muscle tone during a focal impaired-awareness seizure and occurs mostly in people with TLE[8,47]. Besides IA, ictal syncope can also result from systemic vasodilation with a subsequent drop in blood pressure (vasodepressive syncope) or from a combination of seizure-related cardioinhibition and vasodepression[48]. Because awareness is impaired during these seizures, individuals with IA cannot act on the classic prodromal symptoms of syncope, thereby increasing the risk of serious injuries. Indeed, sudden falls and injuries are commonly reported by people with IA, with an average rate of around three falls per month in one case series[49,50].

The high risk of IA recurrence and the frequent falls emphasize the need for timely diagnosis and preventive measures. A diagnosis of IA can be challenging, as the patient will typically not recall presyncopal symptoms, and the occurrence of convulsive syncope (stiffening and jerks) is easily misinterpreted as a TCS, especially in the context of TLE[34]. Reports of flaccid falls with injuries and other signs of syncope (for example, intense pallor, stiffening, myoclonic jerks and gasping) during the course of a temporal lobe seizure should, however, prompt further examinations[47] (FIG. 1). Holter ECG, implantable loop recording and/or video-EEG monitoring should be considered, depending on the seizure frequency and clinical context (for example, eligibility for epilepsy surgery). However, not all seizures in individuals with IA will manifest with asystole. The short-term recurrence risk of IA was estimated at 40% (95% confidence interval (CI): 32–50%)[33]. Therefore, the recording of one or

two seizures might not be sufficient to reject a clinical hypothesis of IA, and a larger number of seizures should be recorded[33].

Retrospective studies suggest that IA and ictal syncope can be prevented by improving seizure control using antiseizure medication (ASM) or epilepsy surgery[50–54]. In individuals who are refractory to ASMs and are not suitable candidates for resective epilepsy surgery, pacemaker implantation is advisable to reduce the risk of falls and injuries[50–52,55]. Retrospective case series indicate that pacemakers prevent syncope-related falls in most patients with IA, although individuals with predominant ictal vasodepression might not benefit from these devices[50–52,55,56].

Respiratory manifestations

Polygraphic video-EEG recordings indicate that central apnoea with oxygen desaturation and increased CO_2 levels occurs in around one-third of seizures[57]. Ictal central apnoea is more frequent in temporal than in extratemporal epilepsy[7,9], and the onset of ictal central apnoea in TLE is tightly linked to the time of spread of seizure activity to the temporal lobe contralateral to the seizure onset zone[58]. Direct electrical stimulation during intracranial EEG recordings revealed that transient central apnoea could be elicited by stimulating a limbic–paralimbic network, including the amygdala, hippocampus, anterior parahippocampal and anteromedial fusiform gyri[59] and/or the perisylvian cortex[60].

Implications for diagnostic work-up

Autonomic signs during seizures can aid localization of the seizure onset zone (TABLE 1) and might occur more frequently in epilepsies caused by certain aetiologies. Autonomic signs are most commonly seen in TLE and are often reported in insular epilepsies, although owing to the rarity of the latter epilepsies, controlled studies are lacking[61]. Most people with TLE exhibit at least one autonomic sign during video-EEG recordings[62]. Epigastric sensations, including nausea, bloating, cramping and stomach pain, are the most commonly reported autonomic manifestations in TLE[62]. These visceral symptoms are generally perceived to ascend through the chest to the head. Among people with focal epilepsies, epigastric auras are associated with a 74% probability of TLE[63]. If the epigastric aura evolves into a focal impaired-awareness seizure with oral and manual automatisms, the probability of TLE increases to 98%[63].

Autonomic features might also point towards the epilepsy aetiology. Focal autonomic seizures[64,65] and interictal autonomic dysfunction[66,67] are more frequent in individuals with autoimmune encephalitis than in those with focal epilepsies of unknown cause. Therefore, autoimmune testing should be considered in patients with autonomic symptoms, particularly those with temporal MRI hyperintensities, behavioural changes, cognitive symptoms, speech problems and/or autoimmune diseases[66]. Leucine-rich glioma-inactivated 1 (LGI1) autoimmune encephalitis seems to be particularly strongly associated with ictal piloerection[68]. A survey reported autonomic seizures in up to one-quarter of individuals with LGI1 encephalitis; however, in most cases, these manifestations were not recognized at the initial presentation[69]. Autoimmune encephalitis, in particular *N*-methyl-D-aspartate receptor (NMDAR) encephalitis, can also manifest with interictal autonomic changes[67,70,71]. Autonomic instability, including central hypoventilation and paroxysmal sympathetic hyperactivity, is a frequent reason for intensive care unit admission in people with NMDAR encephalitis[70,71].

Prominent autonomic signs are also common in certain epilepsy syndromes, most notably Panayiotopoulos syndrome, in which children may present with autonomic status epilepticus[72]. Other examples include Rett syndrome, *SCN8A*-related encephalopathy and Dravet syndrome. People with Rett syndrome can present with various autonomic abnormalities, including erratic breathing with periodic hypopnea followed by hyperventilation[73]. *SCN8A*-related encephalopathy is characterized by generalized symmetric tonic seizures with prominent and alternating autonomic signs (bradyarrhythmia and tachyarrhythmia, hypoventilation and hyperventilation, and flushing and cyanosis)[74]. Peri-ictal respiratory abnormalities, including airway obstruction and ataxic or paradoxical breathing, are more frequent in individuals with Dravet syndrome than in those with focal epilepsy[75]. Depression of CO_2 chemoreception can persist as long as 4 h after the end of a seizure.

Anatomy and physiology of autonomic networks

Various areas throughout the brain — including the amygdala, anterior cingulate, insula, thalamus, hypothalamus, periaqueductal grey matter, parabrachial nucleus and several medullary regions — regulate the central processing of autonomic responses[76] (FIG. 2). This CAN has a crucial role in homeostasis of bodily functions, conscious visceral perception and regulation of emotional responses via the sympathetic and parasympathetic nervous systems[77].

The CAN is a highly integrated, reciprocal, interconnected network that displays task and division specificities. Neuroimaging experiments have revealed that the central processing of autonomic function is mediated by divergent regulatory networks with differential involvement in affective, cognitive and somatosensory–motor tasks[78]. Sympathetic-associated brain regions predominate in executive and salience processing networks, whereas parasympathetic regions have prominent roles in the default mode network. A set of brain regions comprising the left amygdala, right and left insula and midcingulate cortices is consistently activated across all tasks and, thus, constitutes the core of the CAN[78]. The interconnections between the central regions that regulate sympathetic and parasympathetic outflow could explain why seizures with apparently similar ictal onset zones and propagation pathways can evoke contrasting autonomic responses[79].

Seizures are thought to influence CAN function through multiple pathways. In addition to direct activation of the central to peripheral autonomic routes, ictal autonomic alterations might result from reflex responses to the behavioural effects of seizures (FIG. 3) and from the effects of catecholamines released by the adrenal glands[8,80]. The occurrence of oscillatory heart rate patterns during

the course of a seizure might point towards interference of such reflexes with the direct pathway[79].

Many non-seizure-related factors modulate the ictal autonomic response, and the extent of the ictal alterations depends on the integrity of the ANS. People with epilepsy frequently display blunted interictal HRV[81], which is thought to reflect reduced vagal and increased sympathetic modulation. Impaired HRV seems to be particularly severe in people with TLE and difficult-to-treat epilepsies[81]. The aetiology of the HRV derangements in epilepsy is unclear, but they could reflect seizure-related or treatment-related effects on the central and peripheral autonomic networks. Some evidence suggests that excessive brainstem atrophy is associated with blunted HRV in focal epilepsy[82]. Functional imaging studies demonstrated abnormalities in key autonomic regulatory brain regions in individuals at high risk of SUDEP[83].

Autonomic alterations following ASM initiation have also been described, although the precise contribution of ASMs to the risk of severe cardiovascular disease and fatal arrhythmias has been a matter for debate[1,30]. The association between ASM use and autonomic function is likely to be multifactorial, with seizure control and specific drug properties as important variables. Sodium channel-blocking ASMs — including carbamazepine, lacosamide, lamotrigine and phenytoin — might decrease the heart rate, particularly at high dosages[1,30]. Concomitant non-epilepsy medications that affect the ANS, such as β blockers, could also potentially influence ictal autonomic responses, although no studies have formally investigated this possibility. In addition, ageing is known to impair adaptation to physiological stressors[84], but the implications for ictal autonomic changes in people with epilepsy are unknown.

Evidence suggests that the presence of cardiovascular conditions lowers the threshold for seizure-related autonomic complications[85]. For instance, the presence of underlying cardiovascular conditions in people with epilepsy increases the likelihood of developing IA early in the disease course — even in individuals with refractory epilepsy, IA tends to occur at a comparatively late

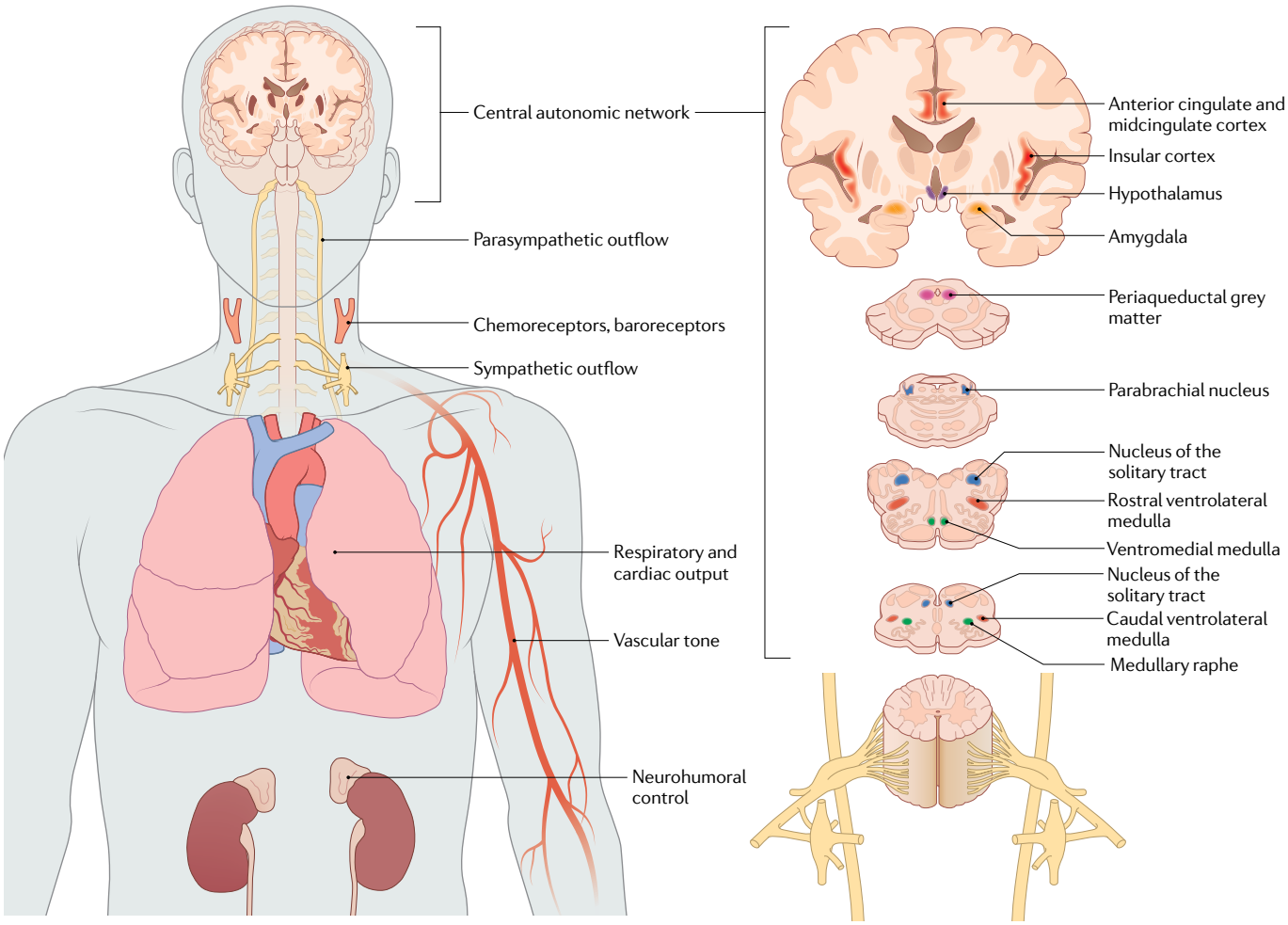

Fig. 2 | **Key autonomic networks involved in cardiovascular and respiratory homeostasis.** Various areas throughout the brain — including the amygdala, anterior cingulate cortex, insular cortex, thalamus, hypothalamus, periaqueductal grey matter, parabrachial nucleus and several medullary regions — regulate central processing of the sympathetic and parasympathetic outflow. The central autonomic network is a highly integrated, reciprocal, interconnected network that controls preganglionic sympathetic and parasympathetic outflow. Cardiovascular and respiratory homeostasis is achieved through multiple feedback loops, including input from baroreceptors, chemoreceptors and pulmonary stretch receptors. Adapted from an original illustration by R. Trompert.

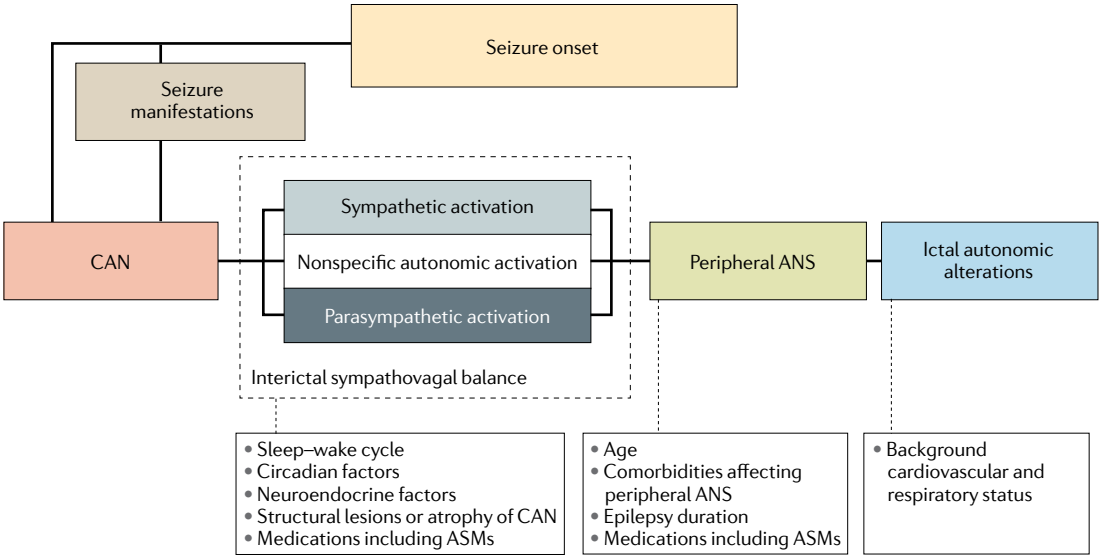

Fig. 3 | **Modulation of the ictal autonomic response.** Schematic diagram illustrating the various factors that might modulate the ictal autonomic response[79]. Seizures can potentially affect the central autonomic network (CAN) through multiple pathways. Besides direct activation of the central to peripheral autonomic routes, ictal autonomic alterations could also result from reflexes in response to the behavioural effects of seizures. Stimulation of the CAN might result in selective sympathetic or parasympathetic activation or nonspecific autonomic activation. The extent of the ictal autonomic response will depend on various clinical determinants, including factors related to the interictal sympathovagal balance, the integrity of the peripheral autonomic nervous system (ANS) and the background cardiovascular and respiratory status. ASMs, antiseizure medications.

stage[85]. These findings suggest that cardiovascular conditions could serve as predisposing factors for early-onset IA in otherwise easy-to-treat epilepsies.

Only a few clinical studies have examined the influence of the sleep–wake cycle and circadian factors on the ictal autonomic patterns[86]. These studies suggested that seizures arising from sleep elicit more prominent autonomic changes than seizures occurring while the individual is awake. Neurohumoral factors might also shape the ictal autonomic response, with some evidence indicating that chronic epilepsy affects the hypothalamic–pituitary–adrenal axis[87]. For instance, the neurohumoral response to acute psychological stress was higher in individuals with left TLE than in healthy controls[88]. Cortisol responses to stress were greater among patients with a higher seizure burden[88].

Autonomic manifestations and sudden death in epilepsy

People with epilepsy have a 24-fold increased risk of dying suddenly compared with the general population[89]. In the general population without epilepsy, SCD is probably the most frequent cause of sudden death among adults, with acute ischaemic events being the main driver[90] (BOX 1). However, sudden death in people with epilepsy tends to occur at a younger age than SCD in the absence of epilepsy, and is not usually associated with overt structural or genetic cardiac pathology[91]. These apparent differences are reflected in the definition of SUDEP as a special category of death (BOX 1).

The exact determination of the underlying mechanisms and the labelling of a sudden death as SUDEP or SCD in a patient with epilepsy can be challenging, given that most cases of sudden death are unwitnessed and post-mortem examinations are often lacking[40,92]. Inevitably, some cases are falsely labelled as SCD or as probable SUDEP, and the potential for overlap between SCD and SUDEP probably goes unrecognized in some patients[40,92]. Indeed, as delineated in BOX 2, some sudden unexpected deaths fulfil the criteria for either SCD (recent and lethal cardiac pathology demonstrated at post-mortem examination) or SUDEP (no lethal cardiac cause previously known or shown at the time of death or at post-mortem examination), whereas others are compatible with both diagnoses (lethal primary cardiac arrhythmia recorded at the time of death but no other known cardiac pathology)[92].

SUDEP incidence and risk factors

The reported incidence of SUDEP varies considerably between studies[93,94]. These discrepancies could be attributable to various confounding factors, including knowledge about SUDEP among health-care professionals and medical coroners, post-mortem policies and structures of national death registries, as well as other inherent limitations of retrospective data collection. In some studies, the incidence of SUDEP in children and adolescents was reported to be much lower than in adults[93,94]; however, research from Canada and Sweden yielded rates of 1.11–1.45 per 1,000 person-years in children and adolescents with epilepsy[95,96], which is similar to the incidence reported in adults with epilepsy (1.20 per 1,000 person-years)[93]. The relatively high incidence in young people might explain why SUDEP ranks second only to stroke in terms of potential life lost due to neurological disorders, despite considerably higher death rates in conditions such as Parkinson disease, stroke and Alzheimer disease[97].

We note that these estimates apply to all people with epilepsy and do not consider the type of epilepsy or disease course. The individual SUDEP risk depends on disease severity and treatment response. In particular, people with medically refractory epilepsies and potential candidates for epilepsy surgery have an higher SUDEP risk than those with well controlled epilepsies[94]. However, SUDEP can occur early in the disease course or in individuals with a condition that is usually considered benign[98,99].

Case–control and epidemiological studies have identified numerous risk factors for SUDEP, the strongest and most consistently reported of which relate to disease severity and seizure activity[94,100]. In particular, TCSs have been linked to elevated risk, with reports of a strong correlation between the number of TCSs per year and SUDEP risk[101–104]. Nocturnal TCSs, but not other types of nocturnal seizures, also predict an increased risk of SUDEP[102]. In addition, lack of nocturnal supervision and living alone are associated with an increased SUDEP risk[102,105,106]. Importantly, accumulation of these risk factors can potentiate the individual risk; for example, people with TCSs who live alone have a 67-fold elevated risk of SUDEP[102].

Proposed pathomechanisms

TCS-triggered cerebral suppression–apnoea–asystole. Most witnessed SUDEP events occur in the aftermath of a TCS[94,107], suggesting that generalized seizure activity triggers pathomechanisms that impair regulation of autonomic pathways and facilitate breakdown of cardiorespiratory function. In fact, all recorded post-ictal SUDEP events that occurred in epilepsy monitoring units under continuous supervision with video, EEG and ECG were preceded by a TCS, followed by a predictable cascade of cardiorespiratory dysfunction[108]. In the aftermath of a TCS, abnormal breathing patterns were observed that eventually developed into periods of apnoea with subsequent episodes of bradycardia and terminal asystole.

Another characteristic feature of the early postictal phase was the generalized flattening of the EEG trace, reflecting PGES[108]. The origin and clinical importance of PGES is not yet fully understood[109], but it seems to be a necessary — though not sufficient — condition for the neurovegetative breakdown in TCS-related SUDEP in humans. In several animal models of genetic epilepsies, PGES occurred in association with a seizure-linked 'depolarization wave', which spread from cortical areas to the brainstem, ultimately suppressing cardiorespiratory brainstem networks[110–113].

Structural and functional imaging studies in people who subsequently died as a result of SUDEP and individuals at high risk of SUDEP identified changes in key central autonomic regulatory regions[114–117]. Ictal autonomic dysfunction might exacerbate deficits in these brain regions, as the extent of brain volume loss among patients with TCS has been linked to the severity of peri-ictal hypoxaemia[118].

Deficits in serotonergic signalling might also be involved in seizure-related breathing disturbances. Animal data suggest that postictal deficits in serotonergic neurotransmission can impair the arousal reaction to postictally elevated CO_2 levels and cause hypoventilation or respiratory arrest[119], which can be prevented by administration of serotonin reuptake inhibitors[120]. In humans, blood serotonin levels were found to be elevated after seizures without ictal or postictal central apnoea but not after seizures with breathing disturbances[121]. Moreover, in a post-mortem study, depletion of brainstem neurons involved in serotonin and galanin signalling was greater in SUDEP cases than in controls[122]. We note that around 75% of people who succumb to SUDEP are found in the prone position, which is likely to further aggravate postictal breathing disturbances[108,123].

Together, these findings strengthen the notion that postictal respiratory dysfunction is a key event in the fatal cascade of TCS-triggered SUDEP. The resulting severe hypoxaemia subsequently causes bradycardia and terminal asystole[124], possibly facilitated by impaired activity of cardiorespiratory brainstem neurons. However, the exact mechanisms involved in the transition from a 'usual' to a fatal TCS remain to be elucidated.

Ictal asystole. For many years, IA was thought to be a possible mechanism of SUDEP. However, several observations indicate that IA is not invariably linked to SUDEP. First, IA is triggered by abnormal brain activity, which is in turn terminated by the resulting cerebral hypoperfusion. Hence, it is not surprising that features of IA resemble those of vasovagal syncope, including its benign nature[125]. Second, in one study, all but one of the reported IA cases had self-limiting asystole[8]. In the one case that was not classified as self-limiting, IA lasted for 44 s, after which the patient was successfully resuscitated[126]. The longest episode of IA reported to date spontaneously resolved after 96 s, casting further doubt on a causal link between prolonged IA and SUDEP[127]. Third, two individuals with ictal bradycardia and IA succumbed to SUDEP despite having well functioning cardiac pacemakers[128,129], strengthening the assumption that SUDEP is not attributable to IA. Last, the brain anoxia that results from IA terminates seizure activity, leading to shorter seizure duration without

Box 1 | **Definitions of SCD and sudden SUDEP**

Sudden cardiac death

Sudden cardiac death (SCD) refers to sudden and unexpected death occurring within 1 h of the onset of symptoms or occurring in patients found dead within 24 h of being asymptomatic, and presumably due to a cardiac arrhythmia or haemodynamic catastrophe[178].

Sudden unexpected death in epilepsy

Sudden unexpected death in epilepsy (SUDEP) is a category of death in people with epilepsy that occurs under benign circumstances and in the absence of known structural causes of death, that is, not due to drowning, injury, intoxication or other internal or external factors[179]. Evidence of a preceding seizure may or not may not be present. 'Definite SUDEP' is confirmed if a post-mortem examination does not reveal an alternative cause of death. If no post-mortem report is available but potentially lethal alternative causes have been excluded and all other criteria are met, the death is labelled as 'probable SUDEP'. The term 'possible SUDEP' is used in cases with competing causes of death or where data are insufficient to reasonably allow classification of the cause of death. The term 'SUDEP plus' applies when a patient also had other diseases that might have contributed to the death but there are no clues that the alternative condition has truly caused it. Cases in which cardiopulmonary resuscitation prevented the death are termed 'near-SUDEP'[179].

Box 2 | **Constellations of sudden death in epilepsy**

We propose the following classification system for the various potentially overlapping constellations of sudden unexpected death in epilepsy (SUDEP) and sudden cardiac death (SCD).

SUDEP and not SCD
Sudden unexpected death without a previously known lethal cardiac cause shown at the time of death or demonstrated at post-mortem examination.

SUDEP and SCD
Sudden unexpected death with a lethal primary cardiac arrhythmia recorded at the time of death and no other known cardiac pathology.

SUDEP plus and not SCD
Sudden unexpected death with a previously known cardiac pathology but no recent and lethal cardiac event recorded during the event or demonstrated at post-mortem examination.

SCD and not SUDEP
Sudden unexpected death with recent and lethal cardiac pathology demonstrated at post-mortem examination.

development to bilateral TCS, which is likely to reduce the risk of SUDEP[55,130].

TCS-triggered ventricular tachycardia and fibrillation. A rare and possibly under-reported SUDEP mechanism was documented in a monitored patient who experienced sudden onset of VT/VF following a focal-to-bilateral TCS. This event was labelled as near-SUDEP, as the patient was successfully resuscitated. Another four cases of VT/VF occurring in the aftermath of a TCS were reported and were labelled as near-SUDEP or SUDEP[30]. No cardiac pathologies were found in these patients, suggesting that the VT/VF was triggered by seizure-related alterations in cardiac properties. VT/VF and SCD are known to be facilitated by cardiac repolarization abnormalities, including prolonged or shortened QT intervals, as well as increased levels of QT dispersion and T-wave alternans[131,132].

Importantly, abnormal cardiac repolarization features are frequently found in people with chronic epilepsy, both in the interictal period and in association with seizures[30,133]. Transient, profound alterations of QT intervals and T-wave alternans are especially common in association with TCS[17,134], probably owing to excessive catecholamine release and strong sympathetic activation[25]. This observation provides a plausible explanation for the sudden onset of VT/VF in the aftermath of a TCS in people without apparent cardiac disease. In a community-based study, the risk of VT/VF was found to be threefold higher in patients with epilepsy than in the general population[135]. Most of the VT/VF events occurred in patients with pre-existing or acute heart conditions[40]. Some cases, however, remained unexplained and could be classified as SUDEP or near-SUDEP, supporting the idea of a partial overlap between SUDEP and SCD[40].

Interictal ventricular tachycardia and fibrillation. Eyewitness reports suggest that around 10% of witnessed SUDEP events occur in the absence of apparent seizure activity[107,136], indicating that seizures are not required as proximate triggers for SUDEP. It is reasonable to assume that in some or even most of these cases, sudden death was caused by cardiac arrhythmias. This assumption is supported by findings that most cases of sudden cardiac arrest in epilepsy occur without evidence of a preceding seizure[40,137], and that cardiac comorbidities are particularly prevalent among people with epilepsy[30,138,139]. For instance, the combined 2010, 2013 and 2015 US National Health Interview Surveys indicated that adults with a history of epilepsy more often report heart disease (21%) than those without such a history (12%)[139]. Accordingly, people with chronic epilepsy frequently display established predictors of cardiac mortality and SCD (for example, impaired HRV and abnormal cardiac repolarization indices) in the interictal period[30,81].

These interictal alterations could relate to the comorbid heart conditions but could also result from incremental subtle damage of cardiac tissue caused by repeated seizures and related cardiotoxic catecholamine release, hypoxaemia, and inflammatory and metabolic factors[30,91]. The structural correlates of such repetitive micro-injuries might be perivascular and interstitial fibrotic microlesions in the heart, which are found in around one-third of patients with epilepsy who undergo a post-mortem examination[91,140]. These seizure-related cardiac changes could help explain why ECG measures of ventricular function, such as myocardial strain and left systolic or diastolic ventricular function, were found to be impaired in people with epilepsy without any known cardiovascular disease[141–143].

A rarer cause of seizure-mediated ventricular dysfunction in epilepsy is the Takotsubo syndrome (also known as apical ballooning), which is characterized by acute onset of heart failure[1,30]. Case series suggest that this syndrome is strongly linked to TCS and the related excessive release of catecholamines[1,30]. Animal studies of acquired epilepsies also revealed modified expression levels of cardiac ion channels (for example, SCN1A, SCN5A and HCN2), leading to altered electrical properties of the heart[144].

The acquired cardiac changes described above are all likely to cause or contribute to disturbed excitation, conduction and repolarization of the heart, thereby serving as potential catalysts for the generation and maintenance of fatal arrhythmias. The concept that the heart and coronary vasculature are incrementally damaged by repeated seizures, resulting in electrical and mechanical dysfunction, has been termed 'epileptic heart'[91].

In addition to acquired alterations of cardiac properties, genetic defects might contribute to both epilepsy and cardiac arrhythmias in some individuals. Potential contributors to 'cardiocerebral' channelopathies include the spectrum of mutations in long QT syndrome genes (for example, *SCN5A*, *KCNQ1* and *KCNH2*) and some gene mutations typically associated with epilepsy (for example, *SCN8A*, *CDKL5*, *CNTNAP2* and *GRIN2A*)[30,145,146]. Some of these mutations have been found in people who succumbed to SUDEP, emphasizing the possible contribution of cardiocerebral phenotypes to SUDEP[146,147].

Interictal cerebral suppression–apnoea–asystole. Interictal cardiorespiratory dysfunction might contribute to the heterogeneity and complexity of SUDEP pathogenesis.

QT intervals
The time from the beginning of the QRS complex to the end of the T wave.

QT dispersion
The difference between the longest and the shortest QT intervals on a 12-lead ECG recording.

In two individuals during and shortly after intracranial EEG recording and in one individual in the context of probable pneumonia during scalp EEG recordings, sudden death was preceded by fluctuating breathing and heart rate and generalized EEG flattening without apparent seizure activity[148]. The sequence and characteristics of the events leading to death in these individuals resembled those of the TCS-triggered cascade described above, prompting the hypothesis of non-seizure-related primary suppression of brainstem activity, affecting respiratory function.

Summary. The evidence outlined above indicates that SUDEP is predominantly caused by TCS-triggered postictal apnoea and asystole, with other mechanisms accounting for a small proportion of cases (FIG. 4). A fixed sequence of apnoea followed by asystole has been observed; no case has yet been reported with asystole but no apnoea. In view of the many facets of interictal and seizure-related cardiovascular and respiratory autonomic alterations, the pathophysiology of sudden death in people with epilepsy is likely to be heterogeneous. Acquired or genetic alterations in autonomic networks, neuronal signalling and cardiac properties contribute to an elevated risk of sudden death. It is important to distinguish SUDEP from SCD, although these entities partially overlap (BOX 2) and might be incorrectly labelled owing to a lack of post-mortem evidence or witnessing of the death.

Prevention of sudden death in epilepsy

The prevention of SUDEP and SCD is an important objective for the epilepsy field. Unfortunately, no randomized controlled trial or other high-quality evidence is currently available to support the effectiveness of a specific intervention for preventing these events[30,93,149,150]. However, some preliminary evidence suggests that improving seizure control and nocturnal supervision can reduce SUDEP risk, which might explain why access to specialized epilepsy services is associated with incremental reductions in the hazard of premature mortality[151].

TCS-related SUDEP

The role of TCS in the chain of events that directly lead to SUDEP in the majority of cases[108] strongly suggests that the better the control of TCS, the lower the SUDEP risk. Accordingly, non-adherence to ASMs and lack of ASM prescription, both of which carry a substantial risk of breakthrough TCS, were found to be associated with an increased risk of SUDEP[93,102]. Furthermore, in a Swedish nationwide case–control study, ASM polytherapy was found to be slightly more protective than monotherapy when the data were adjusted for TCS frequency[102]. Similarly, in a meta-analysis of phase III randomized controlled trials of add-on ASM, individuals who received an additional ASM had a sevenfold-lower incidence of SUDEP than those allocated to add-on placebo[152].

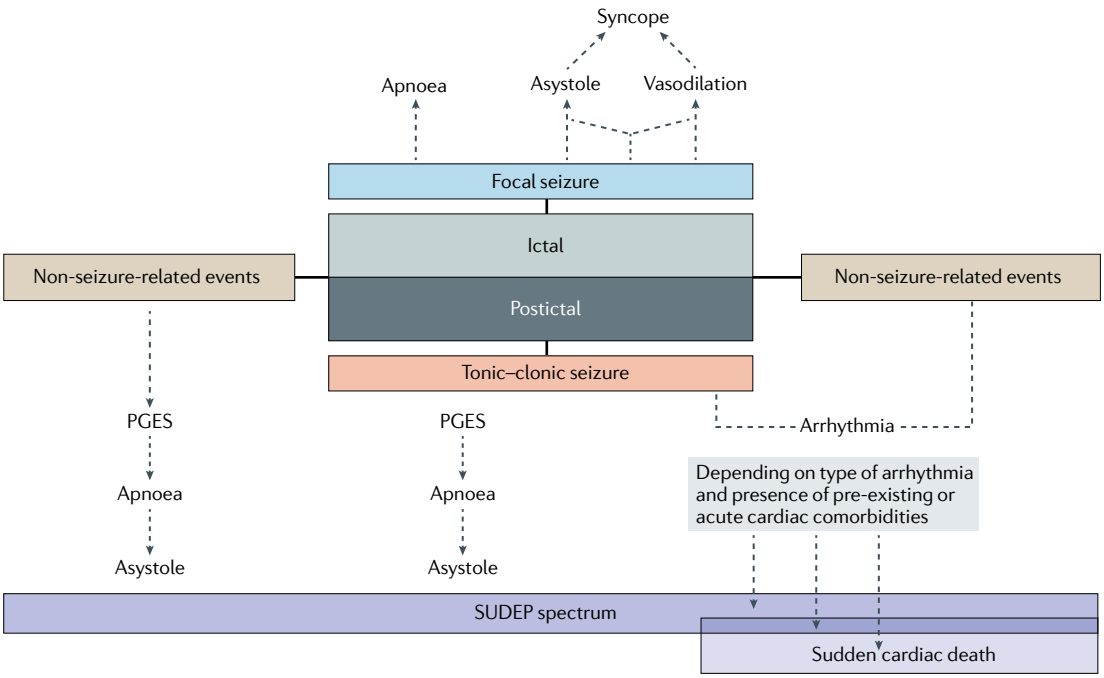

Fig. 4 | **Key pathophysiological events in the SUDEP cascade.** Sudden unexpected death in epilepsy (SUDEP) has a spectrum of heterogeneous causes but is predominantly attributable to tonic–clonic seizure (TCS)-triggered postictal apnoea–asystole. Less-frequent causes can include the sequence of cerebral suppression–apnoea–asystole without a preceding seizure, or seizure-related or non-seizure-related arrhythmias. SUDEP and sudden cardiac death (SCD) are partly overlapping entities, and the presence of pre-existing or acute cardiac comorbidities might help to differentiate between these two events. SUDEP contrasts with self-limiting autonomic features as it is strongly linked to TCSs, whereas ictal apnoea and ictal asystole are associated with focal — mostly temporal lobe — seizures. Another contrast concerns the timing of the event: SUDEP typically occurs in the aftermath of a TCS, and ictal manifestations of asystole or apnoea have not been linked to SUDEP. PGES, postictal generalized EEG suppression.

With regard to surgical interventions, the aforementioned Swedish study found that vagus nerve stimulation was associated with a reduced SUDEP risk[102], consistent with evidence that SUDEP incidence in patients treated with vagus nerve stimulation decreases as a function of treatment duration[153]. The impact of epilepsy surgery on the risk of SUDEP is more controversial[93,154]: lower mortality rates were observed in successful versus failed TLE surgery[155–158], but comparisons of operated and non-operated individuals produced conflicting results[102,159]. Overall, promotion of treatment adherence and state-of-the-art practice guidelines to decrease TCS seems to be an appropriate approach, despite a lack of high-quality evidence that such practices will prevent SUDEP[149].

A Cochrane Review and the American Academy of Neurology–American Epilepsy Society SUDEP guidelines concluded that only very-low-certainty (Grading of Recommendations Assessment, Development and Evaluation) and level C (modified Grading Recommendations Assessment) evidence was available to support the preventive impact of nocturnal supervision on SUDEP risk[93,150]. This evidence was derived from retrospective case–control studies[102,105,106,160] and is supported by the observation that the majority of SUDEP events occur at night, during sleep in non-supervised individuals[101,108,136]. Epilepsy monitoring unit data from the MORTEMUS study also suggest that an immediate nonspecific postictal intervention from a caregiver is likely to prevent SUDEP[108]. Such timely intervention might be promoted by the use of wearable devices that reliably detect TCS and trigger an alarm[161,162] (see below). A retrospective study found reduced SUDEP rates in residential care facilities that offered additional measures to intensify nocturnal supervision[106]. No data are yet available to support the impact of specific TCS-detecting devices on the risk of SUDEP.

A number of other SUDEP prevention methods are being considered with the specific objective of reducing obstructive and/or centrally mediated post-TCS respiratory distress, including lattice pillows, post-ictal O_2 therapy, serotonergic drugs, opiate and adenosine receptor antagonists and implantable devices[149]. Although some animal studies support the value of such interventions to prevent SUDEP, no human study is yet available, and an urgent need exists to develop appropriately designed controlled trials of SUDEP prevention strategies.

Open communication about SUDEP risk, if appropriate, is a particularly important step to prevent SUDEP, as it can promote treatment adherence and guide lifestyle choices, thereby improving seizure control. Various surveys indicate that most people with epilepsy and their families prefer to be informed about SUDEP by their care providers, even if the risk is low[163]. Therefore, the inclusion of SUDEP information is strongly recommended when counselling people with epilepsy and their relatives[93]. Counselling should be tailored to the individual with a view to improving motivation regarding medication adherence or new treatments, as well as allowing other protective measures to be taken (for example, not living or sleeping alone and use of wearable devices) for those at high risk, while avoiding inappropriate fear of SUDEP for those at low risk. Checklists are available to monitor SUDEP risk over time but they cannot provide reliable risk estimates. A recent retrospective study, which used Bayesian models to examine 1,273 individuals with epilepsy, showed that personalized model predictions were superior to population-based estimates for predicting SUDEP[164].

SCD in people with epilepsy

Data regarding prevention of SCD in epilepsy are scarce. As TCS might trigger myocardial injuries or even infarction[1,30], one might expect that reducing TCS would also reduce risk of SCD. The overall risk reduction is likely to be minimal, however, as most SCD events are not linked to seizures[40,137]. In view of the cardiac effects of chronic epilepsy, such as HRV suppression and cardiac repolarization abnormalities[30,91], people with epilepsy are likely to benefit from alternative strategies, including cardiovascular risk assessments and appropriate preventive treatments. Some data indicate that enzyme-inducing ASMs have a negative impact on lipid profiles[30,91], although whether these drugs increase SCD risk in people with epilepsy is not yet known. Genetic screening for cardiocerebral channelopathies should also be considered in individuals with epilepsy who have unexplained arrhythmias[30,145,146].

Wearable devices

Non-invasive wearable devices to improve seizure detection are being developed at a rapid pace. Such devices have an important role in monitoring disease activity, as video-EEG studies have demonstrated that seizure diaries are notoriously unreliable[165]. On average, individuals with epilepsy are thought to report fewer than half of their seizures[165]. Seizure under-reporting is a particular concern in patients with focal impaired-awareness seizures or nocturnal seizures[165].

Improved monitoring might also decrease the risk of seizure-related complications, including SUDEP. Autonomic features are promising targets for seizure detection devices, as these features are very sensitive to physiological stressors. To date, validation studies for these devices have been heterogeneous with regard to the study population, range of seizure type, duration of follow-up, recording settings and the gold standard applied[166,167]. Most studies that have used autonomic features for seizure detection have been pilot or proof-of-principle studies that lack the long-term and real-time ambulatory monitoring that will be needed to obtain reliable performance data and usability outcomes[21]. Various strategies have been applied, including single-modality algorithms based on heart rate, HRV or QRS morphology, and multimodal algorithms using various combinations of heart rate, corrected QT interval, oxygen saturation, electrodermal activity and accelerometry. The best performance is likely to be achieved if autonomic modalities are combined, because single-modality algorithms yield unacceptably high false-alarm rates[21]. Standards for testing and validation of seizure detection devices have been proposed in an attempt to increase study quality[167].

Fifteen studies of phase II or above have demonstrated that non-EEG seizure detection devices (including autonomic and non-autonomic sensors) can detect the occurrence of TCS with high sensitivity (≥90%) and low false-alarm rates (down to 0.2 per day)[166]. Detection of non-convulsive seizures is more challenging, as the most frequently applied autonomic modalities — heart rate and electrodermal activity — fail to reliably distinguish these events from other physiological stressors. HRV measures might provide an alternative approach to detect these seizures[168,169]. A recent phase II study demonstrated the feasibility of such an approach in individuals with marked ictal autonomic changes, characterized by an increase in heart rate of more than 50 bpm (REF.[169]). The HRV algorithm had a sensitivity of 90% with variable false-alarm rates (overall 1.0 per 24 h, night-time 0.1 per night). Pulse wave features other than heart rate and HRV can also be extracted from photoplethysmography and might display specific changes before, during and after focal impaired-awareness seizures[170]. Machine-learning techniques are another important avenue to explore to improve detection of non-convulsive seizures[171].

Various surveys have highlighted considerable interest in the use of wearable technology across the epilepsy community[172]. User studies indicated that removable but securely fitted, wireless and comfortable wearable devices are preferred for seizure detection[173]. Long-term home-based trials are needed to explore the added value of these devices. Autonomic interventions can also be applied via neuromodulation devices. Application of additional vagus nerve stimulation pulses triggered by seizure-related increases in heart rate might alleviate seizure severity[174].

Conclusions and future perspectives

As discussed in this Review, the field of autonomic dysfunction in epilepsy has proved to be extremely rich, complex and relevant to the most severe outcomes affecting persons with epilepsy, including premature and sudden death (SCD or SUDEP). However, our understanding of many aspects of interictal and peri-ictal autonomic changes associated with seizure disorders remains limited, and more research is required. In particular, large-scale epilepsy monitoring unit studies are needed to comprehensively assess all relevant neurovegetative functions and their alterations in epilepsy. In addition, researchers can take advantage of the rapidly developing field of health-directed wearable devices, including seizure detectors, to conduct ambulatory studies. Wearable devices are particularly attractive in view of their potential to grade seizure severity over time and to capture circadian changes in autonomic control (for example, sleep-to-awake HRV)[15,161,175]. Epilepsy cohorts need to be large enough to enable prospective case–control studies of the most relevant clinical end points, including sudden death.

Specific investigations should also focus on the long-term impact of medical and surgical epilepsy treatments on cardiovascular function and mortality, especially in elderly individuals and patients with late-onset epilepsy, who have the greatest risks of cardiovascular complications. Further exploration of the central regulation of autonomic functions and its disorders in people with epilepsy, taking advantage of the neuroimaging, neurophysiology (including intracerebral EEG) and genetic investigations performed in this population, should also be encouraged. Besides acquiring new knowledge, efforts should be made to provide evidence-based practice guidelines for autonomic investigations in people with epilepsy. In particular, recommendations are needed regarding the clinical indications for basic and more sophisticated cardiovascular explorations. Finally, controlled trials are urgently needed to test the impact of various interventions on the risk of premature death, SCD and SUDEP, including usage of readily available seizure detection devices and other methods of nocturnal supervision.

Published online 29 October 2021

1. Shmuely, S., van der Lende, M., Lamberts, R. J., Sander, J. W. & Thijs, R. D. The heart of epilepsy: current views and future concepts. *Seizure* **44**, 176–183 (2017).
2. Baumgartner, C., Koren, J., Britto-Arias, M., Schmidt, S. & Pirker, S. Epidemiology and pathophysiology of autonomic seizures: a systematic review. *Clin. Auton. Res.* **29**, 137–150 (2019).
3. Russell, A. E. Cessation of the pulse during the onset of epileptic fits, with remarks on the mechanism of fits. *Lancet* **168**, 152–154 (1906).
4. Fisher, R. S. et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* **58**, 531–542 (2017).
5. Fisher, R. S. et al. Classification as autonomic versus sensory seizures. *Epilepsia* **60**, 2003–2005 (2019).
6. Mielke, H., Meissner, S., Wagner, K., Joos, A. & Schulze-Bonhage, A. Which seizure elements do patients memorize? A comparison of history and seizure documentation. *Epilepsia* **61**, 1365–1375 (2020).
7. Lacuey, N. et al. The incidence and significance of periictal apnea in epileptic seizures. *Epilepsia* **59**, 573–582 (2018).
8. van der Lende, M., Surges, R., Sander, J. W. & Thijs, R. D. Cardiac arrhythmias during or after epileptic seizures. *J. Neurol. Neurosurg. Psychiat.* **87**, 69–74 (2016).
9. Vilella, L. et al. Incidence, recurrence, and risk factors for peri-ictal central apnea and sudden unexpected death in epilepsy. *Front. Neurol.* **10**, 166 (2019).
10. Eggleston, K. S., Olin, B. D. & Fisher, R. S. Ictal tachycardia: the head–heart connection. *Seizure* **23**, 496–505 (2014).
11. Brugada, J. et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC): developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur. Heart J.* **41**, 655–720 (2020).
12. Jeppesen, J., Beniczky, S., Johansen, P., Sidenius, P. & Fuglsang-Frederiksen, A. Comparing maximum autonomic activity of psychogenic non-epileptic seizures and epileptic seizures using heart rate variability. *Seizure* **37**, 13–19 (2016).
13. Jeppesen, J., Beniczky, S., Johansen, P., Sidenius, P. & Fuglsang-Frederiksen, A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. *Seizure* **24**, 1–7 (2015).
14. Bruno, E., Biondi, A. & Richardson, M. P. Pre-ictal heart rate changes: a systematic review and meta-analysis. *Seizure* **55**, 48–56 (2018).
15. Beniczky, S., Arbune, A. A., Jeppesen, J. & Ryvlin, P. Biomarkers of seizure severity derived from wearable devices. *Epilepsia* **61** (Suppl. 1), S61–S66 (2020).
16. Sivathamboo, S. et al. Cardiorespiratory and autonomic function in epileptic seizures: a video-EEG monitoring study. *Epilepsy Behav.* **111**, 107271 (2020).
17. Surges, R., Scott, C. A. & Walker, M. C. Enhanced QT shortening and persistent tachycardia after generalized seizures. *Neurology* **74**, 421–426 (2010).
18. Chouchou, F. et al. The neural bases of ictal tachycardia in temporal lobe seizures. *Clin. Neurophysiol.* **128**, 1810–1819 (2017).
19. Page, T. & Rugg-Gunn, F. J. Bitemporal seizure spread and its effect on autonomic dysfunction. *Epilepsy Behav.* **84**, 166–172 (2018).
20. Surges, R., Jordan, A. & Elger, C. E. Ictal modulation of cardiac repolarization, but not of heart rate, is lateralized in mesial temporal lobe epilepsy. *PLoS ONE* **8**, e64765 (2013).
21. van Westrhenen, A., De Cooman, T., Lazeron, R. H. C., Van Huffel, S. & Thijs, R. D. Ictal autonomic changes as a tool for seizure detection: a systematic review. *Clin. Auton. Res.* **29**, 161–181 (2019).
22. Hirsch, M., Altenmüller, D. M. & Schulze-Bonhage, A. Latencies from intracranial seizure onset to ictal tachycardia: a comparison to surface EEG patterns and other clinical signs. *Epilepsia* **56**, 1639–1647 (2015).
23. Stefanidou, M., Carlson, C. & Friedman, D. The relationship between seizure onset zone and ictal tachycardia: an intracranial EEG study. *Clin. Neurophysiol.* **126**, 2255–2260 (2015).
24. Hampel, K. G., Jahanbekam, A., Elger, C. E. & Surges, R. Seizure-related modulation of systemic

arterial blood pressure in focal epilepsy. *Epilepsia* **57**, 1709–1718 (2016).
25. Nass, R. D., Hampel, K. G., Elger, C. E. & Surges, R. Blood pressure in seizures and epilepsy. *Front. Neurol.* **10**, 501 (2019).
26. Hampel, K. G., Elger, C. E. & Surges, R. Impaired baroreflex sensitivity after bilateral convulsive seizures in patients with focal epilepsy. *Front. Neurol.* **8**, 210 (2017).
27. Bozorgi, A. et al. Significant postictal hypotension: expanding the spectrum of seizure-induced autonomic dysregulation. *Epilepsia* **54**, e127–e130 (2013).
28. Lacuey, N. et al. Cortical structures associated with human blood pressure control. *JAMA Neurol.* **75**, 194–202 (2018).
29. Surges, R., Thijs, R. D., Tan, H. L. & Sander, J. W. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat. Rev. Neurol.* **5**, 492–504 (2009).
30. Surges, R., Shmuely, S., Dietze, C., Ryvlin, P. & Thijs, R. D. Identifying patients with epilepsy at high risk of cardiac death: signs, risk factors and initial management of high risk of cardiac death. *Epileptic Disord.* **23**, 17–39 (2021).
31. Mangrum, J. M. & DiMarco, J. P. The evaluation and management of bradycardia. *N. Engl. J. Med.* **342**, 703–709 (2000).
32. Brignole, M. et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur. Heart J.* **39**, 1883–1948 (2018).
33. Hampel, K. G., Thijs, R. D., Elger, C. E. & Surges, R. Recurrence risk of ictal asystole in epilepsy. *Neurology* **89**, 785–791 (2017).
34. Rossetti, A. O. et al. Ictal asystole with convulsive syncope mimicking secondary generalisation: a depth electrode study. *J. Neurol. Neurosurg. Psychiat.* **76**, 885–887 (2005).
35. Britton, J. W., Ghearing, G. R., Benarroch, E. E. & Cascino, G. D. The ictal bradycardia syndrome: localization and lateralization. *Epilepsia* **47**, 737–744 (2006).
36. Nei, M., Sperling, M. R., Mintzer, S. & Ho, R. T. Long-term cardiac rhythm and repolarization abnormalities in refractory focal and generalized epilepsy. *Epilepsia* **53**, e137–e140 (2012).
37. van der Lende, M. et al. The yield of long-term electrocardiographic recordings in refractory focal epilepsy. *Epilepsia* **60**, 2215–2223 (2019).
38. Rugg-Gunn, F. J., Simister, R. J., Squirrell, M., Holdright, D. R. & Duncan, J. S. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* **364**, 2212–2219 (2004).
39. Serdyuk, S. et al. Cardiac arrhythmias and sudden unexpected death in epilepsy: results of long-term monitoring. *Heart Rhythm.* **18**, 221–228 (2021).
40. Lamberts, R. J. et al. Sudden cardiac arrest in people with epilepsy in the community: circumstances and risk factors. *Neurology* **85**, 212–218 (2015).
41. Lamberts, R. J. et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. *J. Neurol. Neurosurg. Psychiat.* **86**, 309–313 (2015).
42. Pang, T. D. et al. Cardiac electrical instability in newly diagnosed/chronic epilepsy tracked by Holter and ECG patch. *Neurology* **93**, 450–458 (2019).
43. Verrier, R. L., Nearing, B. D., Olin, B., Boon, P. & Schachter, S. C. Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. *Epilepsy Behav.* **62**, 85–89 (2016).
44. van Dijk, J. G., van Rossum, I. A. & Thijs, R. D. Timing of circulatory and neurological events in syncope. *Front. Cardiovasc. Med.* **7**, 36 (2020).
45. Ammirati, F., Colivicchi, F., Velardi, A. & Santini, M. Prevalence and correlates of syncope-related traumatic injuries in tilt-induced vasovagal syncope. *Ital. Heart J.* **2**, 38–41 (2001).
46. Aydin, M. A. et al. A standardized education protocol significantly reduces traumatic injuries and syncope recurrence: an observational study in 316 patients with vasovagal syncope. *Europace* **14**, 410–415 (2012).
47. Schuele, S. U. et al. Video-electrographic and clinical features in patients with ictal asystole. *Neurology* **69**, 434–441 (2007).
48. Mastrangelo, V. et al. Ictal vasodepressive syncope in temporal lobe epilepsy. *Clin. Neurophysiol.* **131**, 155–157 (2020).
49. Moseley, B. D., Ghearing, G. R., Munger, T. M. & Britton, J. W. The treatment of ictal asystole with cardiac pacing. *Epilepsia* **52**, e16–e19 (2011).
50. Strzelczyk, A. et al. Management and long-term outcome in patients presenting with ictal asystole or bradycardia. *Epilepsia* **52**, 1160–1167 (2011).
51. Bestawros, M. et al. Ictal asystole and ictal syncope: insights into clinical management. *Circ. Arrhythm. Electrophysiol.* **8**, 159–164 (2015).
52. Casciato, S. et al. Ictal asystole in drug-resistant focal epilepsy: two decades of experience from an epilepsy monitoring unit. *Brain Sci.* **10**, 443 (2020).
53. Kohno, R., Abe, H., Akamatsu, N. & Benditt, D. G. Long-term follow-up of ictal asystole in temporal lobe epilepsy: is permanent pacemaker therapy needed? *J. Cardiovasc. Electrophysiol.* **27**, 930–936 (2016).
54. Benditt, D. G., van Dijk, G. & Thijs, R. D. Ictal asystole: life-threatening vagal storm or a benign seizure self-termination mechanism? *Circ. Arrhythm. Electrophysiol.* **8**, 11–14 (2015).
55. Moseley, B. D., Ghearing, G. R., Benarroch, E. E. & Britton, J. W. Early seizure termination in ictal asystole. *Epilepsy Res.* **97**, 220–224 (2011).
56. van Westrhenen, A. et al. Timing of syncope in ictal asystole as a guide when considering pacemaker implantation. *J. Cardiovasc. Electrophysiol.* https://doi.org/10.1111/jce.15239 (2021).
57. Bateman, L. M., Li, C. S. & Seyal, M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain* **131**, 3239–3245 (2008).
58. Seyal, M. & Bateman, L. M. Ictal apnea linked to contralateral spread of temporal lobe seizures: intracranial EEG recordings in refractory temporal lobe epilepsy. *Epilepsia* **50**, 2557–2562 (2009).
59. Lacuey, N., Hampson, J. P., Harper, R. M., Miller, J. P. & Lhatoo, S. Limbic and paralimbic structures driving ictal central apnea. *Neurology* **92**, e655–e669 (2019).
60. Loizon, M. et al. Transient hypoxemia induced by cortical electrical stimulation: a mapping study in 75 patients. *Neurology* **94**, e2323–e2336 (2020).
61. Jobst, B. C. et al. The insula and its epilepsies. *Epilepsy Curr.* **19**, 11–21 (2019).
62. Janszky, J. et al. Peri-ictal vegetative symptoms in temporal lobe epilepsy. *Epilepsy Behav.* **11**, 125–129 (2007).
63. Henkel, A., Noachtar, S., Pfänder, M. & Lüders, H. O. The localizing value of the abdominal aura and its evolution: a study in focal epilepsies. *Neurology* **58**, 271–276 (2002).
64. Rocamora, R. et al. Pilomotor seizures: an autonomic semiology of limbic encephalitis? *Seizure* **23**, 670–673 (2014).
65. Baysal-Kirac, L. et al. Neuronal autoantibodies in epilepsy patients with peri-ictal autonomic findings. *J. Neurol.* **263**, 455–466 (2016).
66. de Bruijn, M. et al. Antibodies contributing to focal epilepsy signs and symptoms score. *Ann. Neurol.* **89**, 698–710 (2021).
67. Dubey, D. et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* **58**, 1181–1189 (2017).
68. Tényi, D. et al. Ictal piloerection is associated with high-grade glioma and autoimmune encephalitis — results from a systematic review. *Seizure* **64**, 1–5 (2019).
69. van Sonderen, A. et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology* **87**, 1449–1456 (2016).
70. Dalmau, J. et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol.* **18**, 1045–1057 (2019).
71. Yan, L., Zhang, S., Huang, X., Tang, Y. & Wu, J. Clinical study of autonomic dysfunction in patients with anti-NMDA receptor encephalitis. *Front. Neurol.* **12**, 609750 (2021).
72. Ferrie, C. D. et al. Autonomic status epilepticus in Panayiotopoulos syndrome and other childhood and adult epilepsies: a consensus view. *Epilepsia* **48**, 1165–1172 (2007).
73. Singh, J., Lanzarini, E. & Santosh, P. Autonomic dysfunction and sudden death in patients with Rett syndrome: a systematic review. *J. Psychiat. Neurosci.* **45**, 150–181 (2020).
74. Trivisano, M. et al. Generalized tonic seizures with autonomic signs are the hallmark of SCN8A developmental and epileptic encephalopathy. *Epilepsy Behav.* **96**, 219–223 (2019).
75. Kim, Y. et al. Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. *J. Clin. Invest.* **128**, 1141–1153 (2018).
76. Palma, J. A. & Benarroch, E. E. Neural control of the heart: recent concepts and clinical correlations. *Neurology* **83**, 261–271 (2014).
77. Saper, C. B. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* **25**, 433–469 (2002).
78. Beissner, F., Meissner, K., Bär, K.-J. & Napadow, V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J. Neurosci.* **33**, 10503–10511 (2013).
79. Sevcencu, C. & Struijk, J. J. Autonomic alterations and cardiac changes in epilepsy. *Epilepsia* **51**, 725–737 (2010).
80. Nass, R. D. et al. Blood markers of cardiac stress after generalized convulsive seizures. *Epilepsia* **60**, 201–210 (2019).
81. Myers, K. A., Sivathamboo, S. & Perucca, P. Heart rate variability measurement in epilepsy: how can we move from research to clinical practice? *Epilepsia* **59**, 2169–2178 (2018).
82. Mueller, S. G. et al. Brainstem network disruption: a pathway to sudden unexplained death in epilepsy? *Hum. Brain Mapp.* **39**, 4820–4830 (2018).
83. Allen, L. A. et al. Dysfunctional brain networking among autonomic regulatory structures in temporal lobe epilepsy patients at high risk of sudden unexpected death in epilepsy. *Front. Neurol.* **8**, 544 (2017).
84. Lipsitz, L. A. & Novak, V. in *Clinical Autonomic Disorders* (eds Low, P. A. & Benarroch, E. E.) Ch. 12, 164–178 (Lippincott Williams & Wilkins, 2008).
85. Tényi, D. et al. Ictal asystole: a systematic review. *Epilepsia* **58**, 356–362 (2017).
86. Purnell, B. S., Thijs, R. D. & Buchanan, G. F. Dead in the night: sleep-wake and time-of-day influences on sudden unexpected death in epilepsy. *Front. Neurol.* **9**, 1079 (2018).
87. Wulsin, A. C., Solomon, M. B., Privitera, M. D., Danzer, S. C. & Herman, J. P. Hypothalamic–pituitary–adrenocortical axis dysfunction in epilepsy. *Physiol. Behav.* **166**, 22–31 (2016).
88. Allendorfer, J. B. et al. Physiologic and cortical response to acute psychosocial stress in left temporal lobe epilepsy — a pilot cross-sectional fMRI study. *Epilepsy Behav.* **36**, 115–123 (2014).
89. Ficker, D. M. et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology* **51**, 1270–1274 (1998).
90. Hayashi, M., Shimizu, W. & Albert, C. M. The spectrum of epidemiology underlying sudden cardiac death. *Circ. Res.* **116**, 1887–1906 (2015).
91. Verrier, R. L., Pang, T. D., Nearing, B. D. & Schachter, S. C. The epileptic heart: concept and clinical evidence. *Epilepsy Behav.* **105**, 106946 (2020).
92. Devinsky, O. et al. Resolving ambiguities in SUDEP classification. *Epilepsia* **59**, 1220–1233 (2018).
93. Harden, C. et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* **88**, 1674–1680 (2017).
94. Tomson, T., Nashef, L. & Ryvlin, P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol.* **7**, 1021–1031 (2008).
95. Sveinsson, O., Andersson, T., Carlsson, S. & Tomson, T. The incidence of SUDEP: a nationwide population-based cohort study. *Neurology* **89**, 170–177 (2017).
96. Keller, A. E., Whitney, R., Li, S. A., Pollanen, M. S. & Donner, E. J. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology* **91**, e107–e111 (2018).
97. Thurman, D. J., Hesdorffer, D. C. & French, J. A. Sudden unexpected death in epilepsy: assessing the public health burden. *Epilepsia* **55**, 1479–1485 (2014).
98. Verducci, C. et al. SUDEP in the North American SUDEP Registry: the full spectrum of epilepsies. *Neurology* **93**, e227–e236 (2019).
99. Hebel, J. M., Surges, R., Stodieck, S. R. G. & Lanz, M. SUDEP following the second seizure in new-onset epilepsy due to limbic encephalitis. *Seizure* **62**, 124–126 (2018).
100. Pensel, M. C., Nass, R. D., Taubøll, E., Aurlien, D. & Surges, R. Prevention of sudden unexpected death in epilepsy: current status and future perspectives. *Expert. Rev. Neurother.* **20**, 497–508 (2020).
101. Lamberts, R. J., Thijs, R. D., Laffan, A., Langan, Y. & Sander, J. W. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* **53**, 253–257 (2012).
102. Sveinsson, O., Andersson, T., Mattsson, P., Carlsson, S. & Tomson, T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. *Neurology* **94**, e419–e429 (2020).

103. Hesdorffer, D. C. et al. Combined analysis of risk factors for SUDEP. *Epilepsia* **52**, 1150–1159 (2011).
104. Hesdorffer, D. C. et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* **53**, 249–252 (2012).
105. Langan, Y., Nashef, L. & Sander, J. W. Case–control study of SUDEP. *Neurology* **64**, 1131–1133 (2005).
106. van der Lende, M., Hesdorffer, D. C., Sander, J. W. & Thijs, R. D. Nocturnal supervision and SUDEP risk at different epilepsy care settings. *Neurology* **91**, e1508–e1518 (2018).
107. Langan, Y., Nashef, L. & Sander, J. W. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J. Neurol. Neurosurg. Psychiat.* **68**, 211–213 (2000).
108. Ryvlin, P. et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol.* **12**, 966–977 (2013).
109. Bruno, E. & Richardson, M. P. Postictal generalized EEG suppression and postictal immobility: what do we know? *Epileptic Disord.* **22**, 245–251 (2020).
110. Aiba, I. & Noebels, J. L. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. *Sci. Transl. Med.* **7**, 282ra246 (2015).
111. Aiba, I., Wehrens, X. H. & Noebels, J. L. Leaky RyR2 channels unleash a brainstem spreading depolarization mechanism of sudden cardiac death. *Proc. Natl Acad. Sci. USA* **113**, E4895–E4903 (2016).
112. Jansen, N. A. et al. Apnea associated with brainstem seizures in Cacna1a (S218L) mice is caused by medullary spreading depolarization. *J. Neurosci.* **39**, 9633–9644 (2019).
113. Loonen, I. C. M. et al. Brainstem spreading depolarization and cortical dynamics during fatal seizures in Cacna1a S218L mice. *Brain* **142**, 412–425 (2019).
114. Allen, L. A. et al. Cerebellar, limbic, and midbrain volume alterations in sudden unexpected death in epilepsy. *Epilepsia* **60**, 718–729 (2019).
115. Allen, L. A., Harper, R. M., Lhatoo, S., Lemieux, L. & Diehl, B. Neuroimaging of sudden unexpected death in epilepsy (SUDEP): insights from structural and resting-state functional MRI studies. *Front. Neurol.* **10**, 185 (2019).
116. Wandschneider, B. et al. Structural imaging biomarkers of sudden unexpected death in epilepsy. *Brain* **138**, 2907–2919 (2015).
117. Mueller, S. G., Bateman, L. M. & Laxer, K. D. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. *Neuroimage Clin.* **5**, 208–216 (2014).
118. Allen, L. A. et al. Peri-ictal hypoxia is related to extent of regional brain volume loss accompanying generalized tonic–clonic seizures. *Epilepsia* **61**, 1570–1580 (2020).
119. Richerson, G. B. & Buchanan, G. F. The serotonin axis: shared mechanisms in seizures, depression, and SUDEP. *Epilepsia* **52** (Suppl. 1), 28–38 (2011).
120. Tupal, S. & Faingold, C. L. Fenfluramine, a serotonin-releasing drug, prevents seizure-induced respiratory arrest and is anticonvulsant in the DBA/1 mouse model of SUDEP. *Epilepsia* **60**, 485–494 (2019).
121. Murugesan, A. et al. Postictal serotonin levels are associated with peri-ictal apnea. *Neurology* **93**, e1485–e1494 (2019).
122. Patodia, S. et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. *Brain* **141**, 1719–1733 (2018).
123. Liebenthal, J. A., Wu, S., Rose, S., Ebersole, J. S. & Tao, J. X. Association of prone position with sudden unexpected death in epilepsy. *Neurology* **84**, 703–709 (2015).
124. Kato, H., Menon, A. S. & Slutsky, A. S. Mechanisms mediating the heart rate response to hypoxemia. *Circulation* **77**, 407–414 (1988).
125. Schuele, S. U., Bermeo, A. C., Locatelli, E., Burgess, R. C. & Lüders, H. O. Ictal asystole: a benign condition? *Epilepsia* **49**, 168–171 (2008).
126. Lanz, M., Oehl, B., Brandt, A. & Schulze-Bonhage, A. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. *Seizure* **20**, 167–172 (2011).
127. Chaila E, B. J., Tirupathi, S. & Delanty, N. Ictal bradycardia and asystole associated with intractable epilepsy: a case series. *Br. J. Cardiol.* **17**, 245–248 (2010).
128. Bank, A. M., Dworetzky, B. A. & Lee, J. W. Sudden unexpected death in epilepsy in a patient with a cardiac pacemaker. *Seizure* **61**, 38–40 (2018).
129. Surges, R. et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. *Epilepsia* **51**, 233–242 (2010).
130. Schuele, S. U., Bermeo, A. C., Alexopoulos, A. V. & Burgess, R. C. Anoxia-ischemia: a mechanism of seizure termination in ictal asystole. *Epilepsia* **51**, 170–173 (2010).
131. Morita, H., Wu, J. & Zipes, D. P. The QT syndromes: long and short. *Lancet* **372**, 750–763 (2008).
132. Verrier, R. L. et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility — consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *J. Am. Coll. Cardiol.* **58**, 1309–1324 (2011).
133. Surges, R., Taggart, P., Sander, J. W. & Walker, M. C. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. *Epilepsia* **51**, 738–744 (2010).
134. Strzelczyk, A. et al. Postictal increase in T-wave alternans after generalized tonic–clonic seizures. *Epilepsia* **52**, 2112–2117 (2011).
135. Bardai, A. et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. *PLoS ONE* **7**, e42749 (2012).
136. Sveinsson, O., Andersson, T., Carlsson, S. & Tomson, T. Circumstances of SUDEP: a nationwide population-based case series. *Epilepsia* **59**, 1074–1082 (2018).
137. Stecker, E. C. et al. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. *Circ. Arrhythm. Electrophysiol.* **6**, 912–916 (2013).
138. Keezer, M. R., Sisodiya, S. M. & Sander, J. W. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol.* **15**, 106–115 (2016).
139. Zack, M. M. & Luncheon, C. Adults with an epilepsy history, especially those 45 years or older, those with lower family incomes, and those with a history of hypertension, report a history of stroke five times as often as adults without such a history-2010, 2013, and 2015 US National Health Interview Survey. *Epilepsy Behav.* **83**, 236–238 (2018).
140. Devinsky, O. et al. Incidence of cardiac fibrosis in SUDEP and control cases. *Neurology* **91**, e55–e61 (2018).
141. Bilgi, M., Yerdelen, D., Cölkesen, Y. & Müderrisoğlu, H. Evaluation of left ventricular diastolic function by tissue Doppler imaging in patients with newly diagnosed and untreated primary generalized epilepsy. *Seizure* **22**, 537–541 (2013).
142. Fialho, G. L., Pagani, A. G., Wolf, P., Walz, R. & Lin, K. Echocardiographic risk markers of sudden death in patients with temporal lobe epilepsy. *Epilepsy Res.* **140**, 192–197 (2018).
143. Schreiber, J. M. et al. Children with refractory epilepsy demonstrate alterations in myocardial strain. *Epilepsia* **61**, 2234–2243 (2020).
144. Li, M. C. H., O'Brien, T. J., Todaro, M. & Powell, K. L. Acquired cardiac channelopathies in epilepsy: evidence, mechanisms, and clinical significance. *Epilepsia* **60**, 1753–1767 (2019).
145. Auerbach, D. S. et al. Genetic biomarkers for the risk of seizures in long QT syndrome. *Neurology* **87**, 1660–1668 (2016).
146. Coll, M. et al. Targeted next-generation sequencing provides novel clues for associated epilepsy and cardiac conduction disorder/SUDEP. *PLoS ONE* **12**, e0189618 (2017).
147. Bagnall, R. D. et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Ann. Neurol.* **79**, 522–534 (2016).
148. Lhatoo, S. D. et al. Nonseizure SUDEP: sudden unexpected death in epilepsy without preceding epileptic seizures. *Epilepsia* **57**, 1161–1168 (2016).
149. Ryvlin, P., Nashef, L. & Tomson, T. Prevention of sudden unexpected death in epilepsy: a realistic goal? *Epilepsia* **54** (Suppl. 2), 23–28 (2013).
150. Maguire, M. J., Jackson, C. F., Marson, A. G. & Nevitt, S. J. Treatments for the prevention of sudden unexpected death in epilepsy (SUDEP). *Cochrane Database Syst. Rev.* **4**, Cd011792 (2020).
151. Lowerison, M. W. et al. Association of levels of specialized care with risk of premature mortality in patients with epilepsy. *JAMA Neurol.* **76**, 1352–1358 (2019).
152. Ryvlin, P., Cucherat, M. & Rheims, S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol.* **10**, 961–968 (2011).
153. Ryvlin, P. et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia* **59**, 562–572 (2018).
154. Ryvlin, P. & Kahane, P. Does epilepsy surgery lower the mortality of drug-resistant epilepsy? *Epilepsy Res.* **56**, 105–120 (2003).
155. Sperling, M. R., Harris, A., Nei, M., Liporace, J. D. & O'Connor, M. J. Mortality after epilepsy surgery. *Epilepsia* **46** (Suppl. 11), 49–53 (2005).
156. Sperling, M. R., Feldman, H., Kinman, J., Liporace, J. D. & O'Connor, M. J. Seizure control and mortality in epilepsy. *Ann. Neurol.* **46**, 45–50 (1999).
157. Salanova, V., Markand, O. & Worth, R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* **43**, 170–174 (2002).
158. Sperling, M. R., Barshow, S., Nei, M. & Asadi-Pooya, A. A. A reappraisal of mortality after epilepsy surgery. *Neurology* **86**, 1938–1944 (2016).
159. Nilsson, L., Ahlbom, A., Farahmand, B. Y. & Tomson, T. Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia* **44**, 575–581 (2003).
160. Shankar, R. et al. Steps to prevent SUDEP: the validity of risk factors in the SUDEP and seizure safety checklist: a case control study. *J. Neurol.* **263**, 1840–1846 (2016).
161. Ryvlin, P., Ciumas, C., Wisniewski, I. & Beniczky, S. Wearable devices for sudden unexpected death in epilepsy prevention. *Epilepsia* **59** (Suppl. 1), 61–66 (2018).
162. Gutierrez, E. G., Crone, N. E., Kang, J. Y., Carmenate, Y. I. & Krauss, G. L. Strategies for non-EEG seizure detection and timing for alerting and interventions with tonic–clonic seizures. *Epilepsia* **59** (Suppl. 1), 36–41 (2018).
163. Bertinat, A., Kerr, M., Cramer, J. A. & Braga, P. Living safely with epilepsy: a key learning review. *Epileptic Disord.* **22**, 364–380 (2020).
164. Jha, A. et al. Sudden unexpected death in epilepsy: a personalized prediction tool. *Neurology* **96**, e2627–e2638 (2021).
165. Elger, C. E. & Hoppe, C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. *Lancet Neurol.* **17**, 279–288 (2018).
166. Beniczky, S. & Jeppesen, J. Non-electroencephalography-based seizure detection. *Curr. Opin. Neurol.* **32**, 198–204 (2019).
167. Beniczky, S. & Ryvlin, P. Standards for testing and clinical validation of seizure detection devices. *Epilepsia* **59** (Suppl. 1), 9–13 (2018).
168. Jeppesen, J. et al. Seizure detection using heart rate variability: a prospective validation study. *Epilepsia* **61** (Suppl. 1), S41–S46 (2020).
169. Jeppesen, J. et al. Seizure detection based on heart rate variability using a wearable electrocardiography device. *Epilepsia* **60**, 2105–2113 (2019).
170. El Atrache, R. et al. Photoplethysmography: a measure for the function of the autonomic nervous system in focal impaired awareness seizures. *Epilepsia* **61**, 1617–1626 (2020).
171. Beniczky, S., Karoly, P., Nurse, E., Ryvlin, P. & Cook, M. Machine learning and wearable devices of the future. *Epilepsia* **62** (Suppl. 2), S116–S124 (2021).
172. Nasseri, M. et al. Signal quality and patient experience with wearable devices for epilepsy management. *Epilepsia* **61** (Suppl. 1), S25–S35 (2020).
173. Bruno, E. et al. Day and night comfort and stability on the body of four wearable devices for seizure detection: a direct user-experience. *Epilepsy Behav.* **112**, 107478 (2020).
174. Hampel, K. G., Vatter, H., Elger, C. E. & Surges, R. Cardiac-based vagus nerve stimulation reduced seizure duration in a patient with refractory epilepsy. *Seizure* **26**, 81–85 (2015).
175. Myers, K. A. et al. Heart rate variability in epilepsy: a potential biomarker of sudden unexpected death in epilepsy risk. *Epilepsia* **59**, 1372–1380 (2018).
176. Vilella, L. et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). *Neurology* **92**, e171–e182 (2019).
177. Carmenate, Y. I., Gutierrez, E. G., Kang, J. Y. & Krauss, G. L. Postictal stertor: associations with focal and bilateral seizure types. *Epilepsy Behav.* **110**, 107103 (2020).

178. Al-Khatib, S. M. et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm.* **15**, e73–e189 (2018).
179. Nashef, L., So, E. L., Ryvlin, P. & Tomson, T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia* **53**, 227–233 (2012).

Acknowledgements
We thank J. Gert van Dijk for drawing the key semiological features of ictal syncope (Fig. 1) and R. Trompert for providing the neuroanatomical illustrations (Fig. 2). P.R. has received research funding from the EU Horizon 2020 Research and Innovation Programme under grant agreements 785907 (HBP SGA2) and 945539 (HBP SGA3). R.D.T. has received research funding from the Human Measurement Models Programme co-funded by Health ~ Holland, Top Sector Life Sciences & Health and ZonMw under grant agreement 114025101 (Brain@Home).

Author contributions
R.D.T. researched data for the article. All authors contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Competing interests
R.D.T. reports lecture and consultancy fees from Medtronic, Union Chimique Belge (UCB), Theravarance, Novartis, Zogenix and Arvelle and grants from the Dutch National Epilepsy Fund, Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, the AC Thomson Foundation, Medtronic, NewLife Wearables and The Netherlands Organisation for Health Research and Development (grant no. 843002707). P.R. reports lecture and consultancy fees from Arvelle, Eisai, LivaNova, Medtronic, Novartis and UCB Pharma and research grants from the Hassler Foundation (Switzerland), the Swiss National Science Foundation and the European Commission. R.S. reports lecture and consultancy fees from Arvelle, Bial, Angelini, Desitin, Eisai, LivaNova, Novartis, UCB Pharma and UnEEG and research grants from the Boll foundation (Kerpen, Germany), BONFOR research funding (Medical Faculty, University of Bonn, Germany), the Federal Ministry of Education and Research (Germany), the Federal Ministry of Health (Germany), and the Verein zur Förderung der Epilepsieforschung e.V. (Bonn, Germany).

Peer review information
Nature Reviews Neurology thanks R. Verrier and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Review criteria
We searched PubMed and SCOPUS for articles published in English from 1 September 2010 to 1 December 2020, with the keywords 'epilep*', 'autonomic', 'seizure detection' and 'SUDEP'. We selected seminal work, clinical studies with the highest level of evidence or the most recent meta-analysis. We have also included earlier articles and reviews if they were particularly pertinent to the discussion.