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Seizures and brain regulatory systems: Consciousness, sleep, and autonomic systems

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Abstract

Research into the physiological underpinnings of epilepsy has revealed reciprocal relationships between seizures and the activity of several regulatory systems in the brain, including those governing sleep, consciousness and autonomic functions. This review highlights recent progress in understanding and utilizing the relationships between seizures and the arousal or consciousness system, the sleep-wake and associated circadian system, and the central autonomic network.

1 Introduction

Individuals with pharmacologically intractable epilepsy face challenges in everyday activities due to the anticipation and consequences of their unpredictable seizures. Progress in understanding how various brain networks affect, and are affected by, epilepsy has led to improvements in epilepsy care (Segal et al., 2012; Seyal et al., 2013). Regulatory systems known to interact with epileptic networks include the consciousness system, the sleep-wake regulatory system, and the autonomic nervous system, among others. This review highlights recent research into the roles of these systems in understanding and managing epilepsy.

2 The consciousness system

Impairment of consciousness (IoC) during seizures puts patients at a risk for social embarrassment and stigmatization as well as physical dangers, including injury and death, due to falls, drowning, and automobile accidents, among others. Generalized seizures typically lead to IoC. Complex partial seizures also lead to IoC, while simple partial seizures do not. Improved understanding of the short-lived and reversible IoC seen during seizures could also impact progress in the study of other disorders of consciousness such as coma.

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The cortical and subcortical structures implicated in regulating consciousness, including the basal forebrain, hypothalamus, thalamus, upper brainstem, medial frontal, anterior and posterior cingulate, and frontal and temporal-parietal association cortices, are collectively termed the 'consciousness system' (Blumenfeld, 2012). This system subsumes portions of the reticular activating system involved in sleep and arousal, as well as the recently categorized 'default mode network' (Raichle et al., 2001) involved in self-awareness and internal processing during the resting-state. Seizures that result in IoC typically affect brain regions within this system. Understanding how spatially restricted partial seizures can cause IoC remains an unresolved challenge.

2.1 Effect of seizures on consciousness in epilepsy syndromes

Consciousness involves subjective first-hand experiences, referred to as content of consciousness, and observed behavioral manifestations, referred to as level of consciousness (Cavanna and Ali, 2011). While various questionnaires have been designed to quantify IoC based on subjective and objective phenomena, IoC can be difficult to define using patient reports (Sanders et al., 2012).

Imaging studies have been used to determine the involvement of various brain structures in seizure-related IoC. Early studies used positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to map metabolism and blood flow-dependent measures of neural activity. More recent studies utilize functional magnetic resonance imaging (fMRI). However, both metabolism and blood flow measures provide indirect estimates of neuronal activity with poor temporal resolution. On the other hand, EEG has high temporal resolution but low spatial resolution. Simultaneous fMRI/EEG measurements (Formaggio et al., 2011; Flanagan et al., 2014) alleviate some concerns with single imaging modalities. However, some caution is required in interpreting even these dual-mode neuroimaging results and novel techniques that more accurately reflect neuronal activity patterns are necessary (Schwartz and Bonhoeffer, 2001).

2.1.1 Impairment of consciousness (IoC) during generalized seizures—

Generalized tonic-clonic (GTCS) and absence seizures are the seizure types in which ictal IoC has been most rigorously studied (Seri et al., 2011; Blumenfeld, 2012). There is some debate as to whether these seizures are truly generalized in the sense of homogeneous brain involvement or whether involvement is biased towards corticothalamic networks (Meeren et al., 2005; Schindler et al., 2007). This distinction is important as it can help to identify and separate brain structures involved in IoC.

Both level and content of consciousness are altered during GTCS, rendering the patient unresponsive to external stimuli. SPECT imaging of secondarily generalized (Shin et al., 2002; Blumenfeld et al., 2009) and electroconvulsive stimulation-induced seizures (Enev et al., 2007) has revealed a pattern of activation of subcortical structures, including the upper brainstem and the midline, mediodorsal and intralaminar thalamic nuclei, with deactivation of cortical structures, including the prefrontal cortex and the anterior/posterior cingulate.

IoC in absence seizures is less severe than in GTCS and patients may respond to simple tasks. EEG/fMRI studies in humans and animals indicate a similar pattern to GTCS, with

increased activity in the thalamus, insula, and cerebellum and decreased activity in frontal and parietal association cortices, posterior cingulate, and other cortical areas (Archer et al., 2003; Moeller et al., 2010). This pattern has also been associated with interruption of the default mode network (Gotman et al., 2005). Similar patterns of activation and deactivation have been observed during interictal spike-wave discharges without IoC (Li et al., 2009). It is suggested that the magnitude of spike-wave discharges during seizures is related to the degree of IoC in absence epilepsy (Bai et al., 2010; Berman et al., 2010).

2.1.2 IoC during partial seizures—There may be changes in the content of consciousness in simple partial seizures and in both the content and level of consciousness in complex partial seizures. IoC in complex partial seizures is less severe than in GTCS, and some responsiveness to simple tasks may be preserved.

A seizure originating in and spatially constrained to the temporal lobe should theoretically lead to deficits in functions such as memory and emotional salience rather than consciousness. However, human and animal studies have confirmed IoC during complex partial seizures restricted to one hemisphere (Van Paesschen et al., 2003; Mueller et al., 2004; Englot et al., 2008), suggesting that focal seizures can lead to secondary effects on larger brain networks.

IoC in temporal lobe epilepsy (TLE) has been correlated with increased amplitude of frontal delta activity on intracranial EEG recordings (Englot et al., 2010). SPECT imaging shows similar patterns of blood flow changes (Lee et al., 2002; Blumenfeld et al., 2004; Tae et al., 2005) in regions with altered EEG/fMRI activity: increased blood flow to the thalamus, basal ganglia, and upper brainstem and decreased blood flow to bilateral orbitofrontal cortices, anterior/posterior cingulate cortex and frontal and parietal association cortices. As with GTCS and absence seizures, these regions overlap the consciousness system and the default mode network. Enhanced thalamocortical EEG synchrony during these seizures has also been observed (Arthuis et al., 2009).

2.2 Mechanisms of seizure-induced IoC

Two main hypotheses exist for IoC during seizures. The network inhibition hypothesis proposes that focal limbic seizures propagate to and alter function of midline subcortical structures involved in the activating and arousal systems. This leads to decreased activity in the fronto-parietal association cortices (Englot et al., 2009; Blumenfeld, 2012), possibly due to an increase in effective inhibition or a decrease in effective excitation in these networks. This hypothesis is similar to a proposed default mode network deactivation hypothesis (Fahoum et al., 2013).

The global workspace hypothesis (Bartolomei et al., 2014) assumes a similar indirect deactivation of frontal and parietal regions due to altered functioning of the thalamus. In this model, excessive seizure-induced synchronization between thalamus and parietal cortex is responsible for breakdown of normal processing leading to deactivation of other cortical areas.

3 Sleep and the circadian system

Several biological rhythms are thought to influence seizure frequency, including sleep-wake, day/night, circadian, menstrual, and lunar cycles (Ramgopal et al., 2013). Sleep-wake, day/night and circadian cycles are related and often defined ambiguously. Sleep-wake cycles require at a minimum a measurement of cortical activity and motion, muscle, or eye activity. Day/night cycles are defined by light on/off cycles in controlled conditions or time of day in natural conditions. Circadian cycles refer to the body's endogenous light-entrained oscillations, with a period of just over 24 hours. Without a direct measure of endogenous activity, daily rhythms are restricted to day/night specifications. While sleep/wake and day/night cycles frequently overlap with the circadian cycle, they can also change independently.

The sleep and circadian system consists mainly of subcortical brain structures, including the thalamus, hypothalamus, and nuclei of the pons and brainstem (Saper et al., 2005). The suprachiasmatic nuclei in the hypothalamus contain neurons with synchronized sub-cellular gene expression 'clocks' that regulate circadian activity (Yamaguchi et al., 2003). These clocks are modulated by both endogenous and extrinsic variables - including food-intake, body temperature, and light input.

Different sleep states engage different portions of the sleep and circadian network. Non-rapid-eye-movement (NREM) or slow-wave sleep is correlated with reduced activity of certain brainstem nuclei, thalamus and medial prefrontal cortex. REM sleep is associated with enhanced activity of the pons, thalamus, limbic areas, and temporo-occipital cortices and reduced activity of prefrontal cortices (Dang-Vu, 2012).

3.1 Effect of seizures on sleep

Epilepsy often co-occurs with sleep disturbances, including frequent arousals, circadian dysregulation, and obstructive sleep apnea (OSA) (Malow, 2007). OSA affects 10–20% of all patients with epilepsy and successful treatment may reduce seizure frequency in some patients (Segal et al., 2012). Anti-convulsant drugs can affect sleep, both beneficially and detrimentally (Legros and Bazil, 2003; Shvarts and Chung, 2013).

3.2 Effect of sleep rhythms on seizure susceptibility

Many syndromes exhibit a correlation between sleep-wake stage and seizure occurrence. This effect is dependent on the epilepsy syndrome and the location and pathophysiology of the seizure focus (Derry and Duncan, 2013; Ramgopal et al., 2013). NREM sleep has been associated with increased seizure susceptibility, whereas REM sleep is usually regarded as the least seizure-susceptible state. Due to the lack of circadian markers in most studies, the true effect of circadian cycles on seizure frequency is poorly understood (Hofstra and de Weerd, 2009; Mirzoev et al., 2012).

Childhood epilepsy syndromes are frequently associated with increased epileptogenicity during NREM sleep, as seen in continuous spike-waves during sleep (Sanchez Fernandez et al., 2013). Absence seizures preferentially occur during the first phases of NREM sleep (Matos et al., 2010). Seizures in inherited and other frontal lobe epilepsies also occur predominately during NREM sleep. In contrast, seizures in TLE most often occur during

wakefulness, though more partial seizures secondarily generalize during NREM (Sinha, 2011). In juvenile myoclonic epilepsy, seizures predominate at the transition of sleep to wakefulness and seizure frequency increases following nights of sleep deprivation. The modulatory role of sleep deprivation on seizure susceptibility is poorly understood (Malow, 2004; Huber et al., 2013).

3.3 Animal models

An association between sleep and seizure frequency has been established in several animal models, particularly in electrochemical rodent models of TLE. Although these models (pilocarpine, kainic acid, tetanus toxin) all produce seizures originating from the temporal lobes, the anatomical and neurochemical deficits that produce the seizures are different (Sharma et al., 2007). As different patterns of structural damage can have differing effects on the sleep network, direct comparison of sleep and seizure associations across models requires caution. Rodent and human sleep systems are homologous and many important sleep-related findings were discovered in rodent models. However, these systems differ in two important ways: rats are nocturnal and have punctuated sleep-wake cycles, whereas humans are diurnal and sleep in consolidated bouts. Thus, for rats, day/night and sleep-wake cycles do not overlap. This may confound analyses that average over long time periods or do not differentiate between the two rhythms.

Despite these differences, the basic effect of sleep on seizures in humans is also observed in rats (Matos et al., 2013). In models of TLE and absence epilepsy, seizures are more frequent during the day, when rats spend a greater amount of time in sleep, and are more frequent in NREM than REM sleep. However, measures required for accurate disambiguation between sleep states are not routinely incorporated. A recent study (Sedigh-Sarvestani et al., 2014) incorporating head motion activity found that REM sleep preceded a disproportionately large fraction of seizures in the tetanus toxin model of TLE, providing counterevidence for the presumed anti-epileptic role of REM sleep (Shouse et al., 2000; Colom et al., 2006).

3.4 Mechanisms of sleep and seizure co-regulation

Several hypotheses exist to explain the role of sleep-wake state on seizure susceptibility (Sinha, 2011). The prevailing theory is that cortical synchrony during NREM facilitates seizure initiation and spread, while cortical desynchrony during REM prohibits seizure initiation. Systemic neurotransmitters that covary with sleep-wake cycles are also being investigated for their role in seizure susceptibility (Loddenkemper et al., 2011). Adenosine, which rises and falls in concentration during sleep and wakefulness, may have anti-epileptic properties (Boison, 2010). The roles of melatonin and serotonin are also being investigated in relation to sleep (Gholipour et al., 2010; Richerson, 2013).

4 The central autonomic network (CAN)

The CAN is involved in regulation of visceral functions including blood pressure, heart rate, respiration, thermoregulation, and digestion (Benarroch, 1993). Brain structures constituting the CAN include the insula, anterior cingulate, hippocampus, amygdala, hypothalamus, and

regions of the pons and medulla. These areas are reciprocally connected with, and modified by, sleep-wake and circadian cycles.

The observation of autonomic disturbances, such as cardiac arrhythmias and respiratory arrest, accompanying seizures indicates that epileptic activity can disrupt normal functioning of the CAN (Moseley et al., 2013). Most reports indicate an increase in sympathetic and decrease in parasympathetic activity. Animal studies have shown ictal increases in blood pressure and heart rate and increased epinephrine and norepinephrine levels, indicative of increased sympathetic activity (Sevcencu and Struijk, 2010). An imbalance of these systems can be detrimental to overall health, and has been recognized as a potential mechanism contributing to increased risk for sudden unexpected death in epilepsy (Hirsch et al., 2011). Improved understanding of the involvement of the CAN in epilepsy has potential to mitigate adverse epilepsy outcomes resulting from autonomic dysfunction.

4.1 Effect of seizures on CAN

Ictal autonomic disturbances depend on the localization and lateralization of seizure onset and vary greatly between childhood and adult epilepsy syndromes. Autonomic symptoms can be more visible than non-autonomic and localization related symptoms of epileptic activity (Moseley et al., 2013). One of the most notable autonomic epilepsy syndromes is Panayiotopoulos syndrome, a partial seizure disorder occurring in children with ictal vomiting and tachycardia. Autonomic disturbances are also prominent in TLE in both children and adults (Jansen et al., 2013).

Given the variety of potential ictal autonomic disturbances, multiple measures are required to develop a profile of ictal or interictal autonomic impairment. Testing methods employed in clinical and research settings include electrocardiography (EKG), pulse oximetry and respiratory monitors, and galvanic skin response testing (Moseley et al., 2013).

4.1.1 Cardiac function—About one third of epilepsy patients have an abnormal interictal EKG. Ictal tachycardia occurs in a majority of seizures while bradycardia, asystole and other findings, such as ventricular repolarization changes, are noted less frequently (Sevcencu and Struijk, 2010; Moghimi and Lhatoo, 2013). Reduced heart rate variability, an indicator of impaired autonomic integrity and an identified risk factor for mortality in other medical conditions, is seen in some epilepsy patients, particularly those with uncontrolled seizures, and with GTCS (Lotufo et al., 2012).

4.1.2 Respiratory function—Respiratory function is rarely monitored in epilepsy patients, even in epilepsy monitoring units, though this practice is changing. Seizures may be associated with respiratory abnormalities, including apneas, hypopneas, excessive oral and bronchial secretions, laryngospasm or neurogenic pulmonary edema. Hypoxemia and hypercapnia occur commonly in patients with localization related epilepsy, and may be related to seizure spread and generalization (Bateman et al., 2008; Moseley et al., 2011). Both may influence cardiac conduction, thus certain cardiac impairments may be secondary effects of ictal respiratory dysfunction (Seyal et al., 2011). However, the administration of exogenous carbon dioxide reduces seizure duration (Tolner et al., 2011), thus hypercapnia may contribute to seizure termination processes and serve a protective function.

4.1.3 Sudden unexpected death in epilepsy (SUDEP) and its mechanisms—

SUDEP is defined as a "sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus" (Nashef and Brown, 1996). While the definitive pathophysiological mechanisms of SUDEP are not known, leading mechanistic hypotheses include respiratory dysfunction, cardiac arrhythmias, and cerebral electrical shutdown (Surges et al., 2009; Shorvon et al., 2011).

Animal studies provide conflicting data on possible SUDEP mechanisms. In certain channelopathy mouse models, cardiac arrhythmias have been reported in association with fatal seizures (Goldman et al., 2009). Alternately, in mice with fatal audiogenic seizures, and in a sheep model of epileptic death, hypoventilation and central apnea were identified as the primary contributors (Johnston et al., 1995; Faingold et al., 2010). Cases of sudden death have been observed in a colony of captive baboons with naturally-occurring epilepsy, which may provide further insights into human SUDEP (Szabo et al., 2009).

A recent review of SUDEP cases reported from international epilepsy centers (the MORTality in Epilepsy Monitoring Units Study, MORTEMUS) demonstrated a common pattern of post-ictal autonomic dysfunction leading to sudden death. Following a GTCS, a brief period of tachypnea with generalized suppression of the EEG was followed by terminal or transient and subsequently recurring cardiorespiratory failure within three minutes. Apnea always preceded asystole and primary cardiac arrhythmias were not seen (Ryvlin et al., 2013a).

5 Future Directions: Utilizing regulatory system relationships to improve epilepsy care

5.1 Prediction and detection of seizure onset

Accurate prediction of seizures would reduce the anxiety of anticipating their occurrence and allow for improvements in lifestyle, such as driving. It could also facilitate the development of closed-loop brain stimulation devices, which have the advantage of reduced current delivery and increased battery life over existing open-loop devices.

Efforts to predict seizures based on features extracted from the EEG span at least five decades, but to date no accurate and robust prediction algorithm has been developed. At the recent International Workshop on Seizure Prediction (IWSP6), identification and implementation of features based on physiologically relevant modulators of epileptic activity was recommended. Sleep-wake state is the best known modulator of seizure onset but has not been incorporated into any prediction algorithm. In fact, failure to account for sleep-wake state can reduce the accuracy and efficiency of prediction algorithms (Schelter et al., 2006; Mormann et al., 2007). Basic differentiation between sleep and wakefulness can be done from extra or intracranial EEG. Thus it is currently feasible to incorporate instantaneous sleep-wake state determinations into implantable seizure warning devices (Cook et al., 2013).

Detection of seizure onset, compared to its prediction, is a relatively easier task. Many accurate seizure detection algorithms have been developed but their reliance on EEG measurements currently restricts their use. Seizure detection based on measurement of ictal autonomic changes has been demonstrated (Poh et al., 2012; Osorio, 2014) and offers a potential, economically feasible detection strategy for home use. A benefit of such methods in the outpatient setting has yet to be demonstrated, however.

5.2 Reducing seizure frequency with chronoepileptology

Although many patients have seizures influenced by sleep-wake or day/night cycles, these patterns are not routinely used in epilepsy management. Profiling individual seizure susceptibility cycles with the use of seizure diaries or ambulatory EEG, could allow for a medication dosing strategy that matches peaks of seizure susceptibility to peaks of serum levels. This strategy, referred to as chronoepileptology (Ramgopal et al., 2013), may also be used in stimulation devices (Loddenkemper et al., 2011).

The circadian kinetics of anti-convulsant drug absorption and depletion and the effects of these drugs on sleep and circadian cycles must also be considered when developing individualized dosing efforts (Ramgopal et al., 2013). A chronoepileptology approach demonstrated improved seizure control in a recent pilot study (Guilhoto et al., 2011), and additional trials are underway. Continued progress in our understanding of systems that regulate seizure susceptibility could lead to improved seizure prediction algorithms, and thus increase the population of patients who may benefit from chronoepileptology.

5.3 Reducing incidence of SUDEP

Ictal involvement of the CAN likely plays a role in SUDEP. However, the factors that determine whether ictal autonomic dysfunction will be transient with full recovery or terminal leading to SUDEP require further investigation. IoC and failure of normal arousal mechanisms have been linked to SUDEP (Richerson, 2013). SUDEP is thought to occur more frequently during sleep, suggesting a possible causal association. Sleep-related ictal phenomena, such as preferential seizure occurrence and secondary generalization in some populations could favor the pathophysiological mechanisms leading to SUDEP (Nobili et al., 2011; Ramgopal et al., 2012), Sleep-related environmental factors, such as lack of supervision at night, may also play a role (Ryvlin et al., 2013a; Lamberts et al., 2012).

In the MORTEMUS study, patients were successfully rescued from cardiorespiratory arrest if resuscitative efforts were administered within three minutes. SUDEP cases involved delayed or absent resuscitative measures (Ryvlin et al., 2013a). This suggests, albeit with a small sample size, that the incidence of SUDEP may be reduced by mechanisms used to detect seizures or autonomic disturbances and alert caregivers so that potentially life-saving interventions may occur (Poh et al., 2012; Ryvlin et al., 2013b; Seyal et al., 2013).

Conclusions

Incorporation of recent findings on the relationships between sleep, consciousness, and autonomic regulatory networks in epilepsy can be utilized to develop new therapies and improve existing protocols in epilepsy management. Improved understanding of the

functional role of these systems in epilepsy will lead to advances in the prediction, prevention, and management of seizures and their consequences and in turn improve both the quality, and in some cases, the duration of life of patients living with epilepsy.

References

Archer JS, Abbott DF, Waites AB, Jackson GD. fMRI "deactivation" of the posterior cingulate during generalized spike and wave. Neuroimage. 2003; 20(4):1915–22. [PubMed: 14683697]

Arthuis M, Valton L, Regis J, Chauvel P, Wendling F, Naccache L, Bernard C, Bartolomei F. Impaired consciousness during temporal lobe seizures is related to increased long-distance cortical-subcortical synchronization. Brain. 2009; 132(Pt 8):2091–101. [PubMed: 19416952]

Bai X, Vestal M, Berman R, Negishi M, Spann M, Vega C, Desalvo M, Novotny EJ, Constable RT, Blumenfeld H. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. J Neurosci. 2010; 30:5884–93. [PubMed: 20427649]

Bartolomei F, McGonigal A, Naccache L. Alternation of consciousness in focal epilepsy: the global workspace alteration theory. Epilepsy Behav. 2014; 30:17–23. [PubMed: 24103816]

Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain. 2008; 131(Pt 12):3239–45. [PubMed: 18952672]

Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993; 68:988–1001. [PubMed: 8412366]

Berman R, Negishi M, Vestal M, Spann M, Chung M, Bai X, Purcaro M, Motelow JE, Dix-Cooper L, Enev M, Novotny EJ, Constable RT, Blumenfeld H. Simultaneous EEG, fMRI, and behavioral testing in typical childhood absence seizures. Epilepsia. 2010; 51(10):2011–22. [PubMed: 20608963]

Bisulli F, Vignatelli L, Naldi I, Licchetta L, Provini F, Plazzi G, Di Vito L, Ferioli S, Montagna P, Tinuper P. Increased frequency of arousal parasomnias in families with nocturnal frontal lobe epilepsy: a common mechanism? Epilepsia. 2010; 51(9):1852–60. [PubMed: 20477848]

Blumenfeld H, McNally KA, Vanderhill SD, Paige AL, Chung R, Davis K, Norden AD, Stokking R, Studholme C, Novotny EJ, Zubal IG, Spencer SS. Positive and negative network correlations in temporal lobe epilepsy. Cerebral Cortex. 2004; 14:892–902. [PubMed: 15084494]

Blumenfeld H, Varghese GI, Purcaro MJ, Motelow JE, Enev M, McNally KA, Levin AR, Hirsch LJ, Tikofsky R, Zubal IG, Paige AL, Spencer SS. Cortical and subcortical networks in human secondarily generalized tonic-clonic seizures. Bain. 2009; 132(Pt 4):999–1012.

Blumenfeld H. Impaired consciousness in epilepsy. Lancet Neurol. 2012; 11(9):814–26. [PubMed: 22898735]

Boison D. Adenosine dysfunction and adenosine kinase in epileptogenesis. Open Neurosci J. 2010; 4:93–101. [PubMed: 20730044]

Cavanna AE, Ali F. Epilepsy: The quintessential pathology of consciousness. Behav Neurol. 2011; 24(1):3–10. [PubMed: 21447892]

Colom LV, Garcia-Hernandez A, Castaneda MT, Perez-Cordova MG, Garrido-Sanabria ER. Septo-hippocampal networks in chronically epileptic rats: potential antiepileptic effects of theta rhythms generation. J Neurophysiol. 2006; 95(6):3645–53. [PubMed: 16554504]

Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, D'Souza W, Yerra R, Archer J, Litewka L, Hosking S, Lightfoot P, Ruedebusch V, Sheffield WD, Snyder D, Leyde K, Himes D. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patient with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013; 12:563–71. [PubMed: 23642342]

Dang-Vu TT. Neuronal oscillations in sleep: insights from functional neuroimaging. Neuromolecular Med. 2012; 14(3):154–67. [PubMed: 22274804]

Derry CP, Duncan S. Sleep and epilepsy. Epilepsy Behav. 2013; 26(3):394–404. [PubMed: 23465654]

Enev M, McNally KA, Varghese G, Zubal IG, Ostroff RB, Blumenfeld H. Imaging onset and propagation of ECT-induced seizures. Epilepsia. 2007; 48(2):238–44. [PubMed: 17295616]

Englot DJ, Mishra AM, Mansuripur PK, Herman P, Hyder F, Blumenfeld H. Remote effects of focal hippocampal seizures on the rat neocortex. J Neurosci. 2008; 28(36):9066–81. [PubMed: 18768701]

Englot DJ, Modi B, Mishra AM, DeSalvo M, Hyder F, Blumenfeld H. Cortical deactivation induced by subcortical network dysfunction in limbic seizures. J Neurosci. 2009; 29(41):13006–18. [PubMed: 19828814]

Englot DJ, Yang L, Hamid H, Danielson N, Bai X, Marfeo A, Yu L, Gordon A, Purcaro MJ, Motelow JE, Agarwal R, Ellens DJ, Golomb JD, Shamy MC, Zhang H, Carlson C, Doyle W, Devinsky O, Vives K, Spencer DD, Spencer SS, Schevon C, Zaveri HP, Blumenfeld H. Impaired consciousness in temporal lobe seizures: role of cortical slow activity. Brain. 2010; 133:3764–77. [PubMed: 21081551]

Fahoum F, Zelmann R, Tyvaert L, Dubeau F, Gotman J. Epileptic discharges affect the default mode network—FMRI and intracerebral EEG evidence. PLoS One. 2013; 8(6):e68038. [PubMed: 23840805]

Faingold CL, Randall M, Tupal S. DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest. Epilepsy Behav. 2010; 17(4):436–40. [PubMed: 20335075]

Flanagan D, Badawy RA, Jackson GD. EEG-fMRI in focal epilepsy: local activation and regional networks. Clin Neurophysiol. 2014; 125(1):21–31. [PubMed: 23871167]

Formaggio E, Storti SF, Bertoldo A, Manganotti P, Fiaschi A, Toffolo GM. Integrating EEG and fMRI in epilepsy. Neuroimage. 2011; 54(4):2719–31. [PubMed: 21109007]

Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noevels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009; 1(2):2ra6.

Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. PNAS. 2005; 102(42):15236–40. [PubMed: 16217042]

Gholipour T, Ghasemi M, Riazi K, Ghaffarpour M, Dehpour AR. Seizure susceptibility alteration through 5-HT(3) receptor: Modulation by nitric oxide. Seizure. 2010; 19(1):17–22. [PubMed: 19942458]

Guilhoto LM, Loddenkemper T, Vendrame M, Bergin A, Bourgeois BF, Kothare SV. Higher evening antiepileptic drug does for nocturnal and early-morning seizures. Epilepsy Behav. 2011; 20(2): 334–7. [PubMed: 21195032]

Hirsch LJ, Donner EJ, So EL, Jacobs M, Nashef L, Noebels JL, Buchhalter JR. Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. Neurology. 2011; 76(22): 1932–38. [PubMed: 21543734]

Hofstra WA, deWeerd AW. The circadian rhythm and its interaction with human epilepsy: a review of literature. Sleep Rev Med. 2009; 13(6):413–20.

Huber R, Maki H, Rosanova M, Casarotto S, Canali P, Casali AG, Tononi G, Massimini M. Human cortical excitability increases with time awake. Cereb Cortex. 2013; 23(2):332–8. [PubMed: 22314045]

Jansen K, Varon C, Van Huffel S, Lagae L. Ictal and interictal respiratory changes in temporal lobe and absence epilepsy in childhood. Epilepsy Res. 2013; 106:410–6. [PubMed: 23948397]

Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death. Ann Neurol. 1995; 37:531–537. [PubMed: 7717690]

Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk. Epilepsia. 2012; 53(2):253–257. [PubMed: 22192074]

Lee KH, Meador KJ, Park YD, King DW, Murro AM, Pillai JJ, Kaminski RJ. Pathophysiology of altered consciousness during seizures: Subtraction SPECT study. Neurology. 2002; 59(6):841–6. [PubMed: 12297563]

Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med. 2003; 4(1):51–5. [PubMed: 14592360]

Li Q, Luo C, Yang T, Yao Z, He L, Liu L, Xu H, Gong Q, Yao D, Zhou D. EEG-fMRI study on the interictal and ictal generalized spike-wave discharges in patients with childhood absence epilepsy. Epilepsy Research. 2009; 87(2–3):160–8. [PubMed: 19836209]

Loddenkemper T, Lockley SW, Kaleyias J, Kothare SV. Chronobiology of epilepsy: Diagnostic and therapeutic implications of chrono-epileptology. J Clin Neurophysiol. 2011; 28(2):146–53. [PubMed: 21399517]

Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia. 2012; 53(2):272–82. [PubMed: 22221253]

Malow BA. The interaction between sleep and epilepsy. Epilepsia. 2007; 48(S9):36–8. [PubMed: 18047600]

Malow BA. Sleep deprivation and epilepsy. Epilepsy Curr. 2004; 4(5):193–5. [PubMed: 16059497]

Matos G, Andersen ML, do Valle AC, Tufik S. The relationship between sleep and epilepsy: Evidence from clinical trials and animal models. J Neurol Sci. 2010; 295:1–7. [PubMed: 20621798]

Matos G, Tufik S, Scorza FA, Cavalheiro EA, Andersen ML. Sleep and epilepsy: Exploring an intriguing relationship with a translational approach. Epilepsy Behav. 2013; 26(3):405–409. [PubMed: 23394796]

Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. Arch Neurol. 2005; 62(3):371–6. [PubMed: 15767501]

Mirzoev A, Bercovici E, Stewart LS, Cortez MA, Snead OC 3rd, Dersrocher M. Circadian profiles of focal epileptic seizures: a need for reappraisal. Seizure. 2012; 31(6):412–6. [PubMed: 22537415]

Moeller F, LeVan P, Muhle H, Stephani U, Dubeau F, Siniatchkin M, Gotman J. Absence seizures: individualized patterns revealed by EEG-fMRI. Epilepsia. 2010; 51(10):2000–10. [PubMed: 20726875]

Moghimi N, Lhatoo SD. Sudden unexpected death in epilepsy or voodoo heart: analysis of heart/brain connections. Curr Cardiol Rep. 2013; 15(12):424. [PubMed: 24122216]

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain. 2007; 130(Pt 2):314–33. [PubMed: 17008335]

Moseley BD, Wirrell EC, Nickels K, Johnson JN, Ackerman MJ, Britton J. Electrocardiographic and oximetric changes during partial complex and generalized seizures. Epilepsy Res. 2011; 95(3): 237–45. [PubMed: 21561737]

Moseley B, Bateman L, Millichap JJ, Wirrell E, Panayiotopoulos CP. Autonomic epileptic seizures, autonomic effects of seizures, and SUDEP. Epilepsy Behav. 2013; 26(3):375–385. [PubMed: 23099286]

Mueller SG, Laxer KD, Cashdollar N, Flenniken DL, Matson GB, Weiner MW. Identification of abnormal neuronal metabolism outside the seizure focus in temporal lobe epilepsy. Epilepsia. 2004; 45(4):355–66. [PubMed: 15030498]

Nashef L, Brown S. Epilepsy and sudden death. Lancet. 1996; 348:1324–5. [PubMed: 8918270]

Nobili L, Proserpio P, Rubboli G, Montano N, Didato G, Tassinari CA. Sudden unexpected death in epilepsy (SUDEP) and sleep. Sleep Med Rev. 2011; 15(4):237–46. [PubMed: 20951616]

Osorio I. Automated seizure detection using EKG. Int J Neural Syst. 2014; 24(2):1450001. [PubMed: 24475899]

Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, Madsen JR, Picard RW. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. Epilepsia. 2012; 53(5):e93–e97. [PubMed: 22432935]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. PNAS. 2001; 98(2):676–82. [PubMed: 11209064]

Ramgopal S, Thome-Souza S, Loddenkemper T. Chronopharmacology of anti-convulsive therapy. Curr Neurol NeurosciRep. 2013; 13(4):339.

Ramgopal S, Vendrame M, Shah A, Gregas M, Zarowski M, Rotenberg A, Alexopoulos AV, Wyllie E, Kothare SV, Loddenkemper T. Circadian patterns of generalized tonic-clonic evolutions in pediatric epilepsy patients. Seizure. 2012; 21(7):535–539. [PubMed: 22717517]

Richerson GB. Seretonin: The Anti-SuddenDeathAmine? Epilepsy Curr. 2013; 13(5):241–244. [PubMed: 24348119]

Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, Boon P, Crespel A, Dworetzky BA, Høgenhaven H, Lerche H, Maillard L, Malter MP, Marchal C, Murthy JM, Nitsche M, Pataraia E, Rabben T, Rheims S, Sadzot B, Schulze-Bonhage A, Seyal M, So EL, Spitz M, Szucs A, Tan M, Tao JX, Tomson T. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (mortemus): a retrospective study. Lancet Neurol. 2013a; 12(10):966–77. [PubMed: 24012372]

Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: A realistic goal? Epilepsia. 2013b; S2:23–28. [PubMed: 23646967]

Sanchez Fernandez I, Chapman KE, Peters JM, Harini C, Rotenberg A, Loddenkemper T. Continuous spike and waves during sleep: Electroclinical presentation and suggestion for management. Epilepsy Res Treat. 2013:583531. [PubMed: 23991336]

Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. Anesthesiology. 2012; 116(4):946–59. [PubMed: 22314293]

Saper CB, Scammel TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005; 437:1257–63. [PubMed: 16251950]

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Timmer J, Schulze-Bonhage A. Do false predictions of seizures depend on state of vigilance? Epilepsia. 2006; 47(12):2058–70. [PubMed: 17201704]

Schindler K, Leung H, Lehnertz K, Elger CE. How generalised are secondarily “generalised” tonic clonic seizures? J Neurol Neurosrug Physchiatry. 2007; 78(9):993–6.

Schvarts V, Chung S. Epilepsy, antiseizure therapy, and sleep cycle parameters. Epilepsy Res Treat. 2013; 2013:670682. [PubMed: 23997949]

Schwartz TH, Bonhoeffer T. In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex. Nature Medicine. 2001; 7:1063–7.

Sedigh-Sarvestani M, Thuku GI, Sunderam S, Parkar A, Weinstein SL, Schiff SJ, Gluckman BJ. Rapid eye movement sleep and hippocampal theta oscillations precede seizure onset in the tetanus toxin model of temporal lobe epilepsy. J Neurosci. 2014; 34(4):1105–14. [PubMed: 24453303]

Segal E, Vendrame M, Gregas M, Loddenkemper T, Kothare SV. Effect of treatment of obstructive sleep apnea on seizure outcomes in children with epilepsy. Pediatr Neurol. 2012; 46(6):359–62. [PubMed: 22633630]

Seri S, Brazzo D, Thai NJ, Cerquiglini A. Brain mechanisms of altered consciousness in generalized seizures. Behav Neurol. 2011; 24(1):43–6. [PubMed: 21447897]

Sevcencu C, Struijk JJ. Autonomic alterations and cardiac changes in epilepsy. Epilepsia. 2010; 51(5): 725–37. [PubMed: 20067509]

Seyal M, Pascual F, Lee CY, Li CS, Bateman LM. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. Epilepsia. 2011; 52(11):2105–11. [PubMed: 21906052]

Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia. 2013; 54(2):377–82. [PubMed: 23016848]

Sinha SR. Basic mechanisms of sleep and epilepsy. J Clin Neurophysiol. 2011; 28(2):103–10. [PubMed: 21399513]

Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol. 2009; 5(9):492–504. [PubMed: 19668244]

Sharma AK, Reams RY, Jordan WH, Miller MA, Thacker HL, Snyder PW. Mesial temporal lobe epilepsy: pathogenesis, induced rodent models, and lesions. Toxicol Pathol. 2007; 35(7):984–99. [PubMed: 18098044]

Shin WC, Hong SB, Tae WS, Kim SE. Ictal hyperfusion patterns according to the progression of temporal lobe seizures. Neurology. 2002; 58(3):373–80. [PubMed: 11839835]

Shouse MN, Farber PR, Staba RJ. Physiological basis: how NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation. Clin Neurophysiol. 2000; 111:S9–18. [PubMed: 10996550]

Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet. 2011; 378(9808):2028038.

Szabó CA, Knape KD, Leland MM, Feldman J, McCoy KJ, Hubbard GB, Williams JT. Mortality in captive baboons with seizures: a new model for SUDEP? Epilepsia. 2009; 50(8):1995–8. [PubMed: 19389147]

Tae WS, Joo EY, Kim JH, Han SJ, Suh YL, Kim BT, Hong SC, Hong SB. Cerebral perfusion changes in mesial temporal lobe epilepsy: SPM analysis of ictal and interictal SPECT. Neuroimage. 2005; 24(1):101–10. [PubMed: 15588601]

Tolner EA, Hochman DW, Hassinen P, Otahal J, Gaily E, Haglund MM, Kubova H, Schuchmann S, Vanhatalo S, Kaila K. Five percent CO2 is a potent, fast-acting inhalation anticonvulsant. Epilepsia. 2011; 52(1):104–14. [PubMed: 20887367]

Van Paesschen W, Dupont P, Van Driel G, Van Billoen H, Maes A. SPECT perfusion changes during complex partial seizures in patients with hippocampal sclerosis. Brain. 2003; 126(Pt 5):1103–11. [PubMed: 12690050]

Yamaguchi S, Isejima H, Matsuo T, Okura R, Yagita K, Kobayashi M, Okamura H. Synchronization of cellular clocks in the suprachiasmatic nucleus. Science. 2003; 302(5649):1408–12. [PubMed: 14631044]