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Review

Imaging biomarkers of sleep-related hypermotor epilepsy and sudden unexpected death in epilepsy: a review

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ABSTRACT

In recent years, imaging has emerged as a promising source of several intriguing biomarkers in epilepsy, due to the impressive growth of imaging technology, supported by methodological advances and integrations of post-processing techniques.

Bearing in mind the mutually influencing connection between sleep and epilepsy, we focused on sleep-related hypermotor epilepsy (SHE) and sudden unexpected death in epilepsy (SUDEP), aiming to make order and clarify possible clinical utility of emerging multimodal imaging biomarkers of these two epilepsy-related entities commonly occurring during sleep.

Regarding SHE, advanced structural techniques might soon emerge as a promising source of diagnostic and predictive biomarkers, tailoring a targeted therapeutic (surgical) approach for MRI-negative subjects. Functional and metabolic imaging may instead unveil SHE's extensive and night-related altered brain networks, providing insights into distinctions and similarities with non-epileptic sleep phenomena, such as parasomnias.

SUDEP is considered a storm that strikes without warning signals, but objective subtle structural and functional alterations in autonomic, cardiorespiratory, and arousal centers are present in patients eventually experiencing SUDEP. These alterations could be seen both as susceptibility and diagnostic biomarkers of the underlying pathological ongoing loop ultimately ending in death.

Finally, given that SHE and SUDEP are rare phenomena, most evidence on the topic is derived from small single-center experiences with scarcely comparable results, hampering the possibility of performing any meta-analytic approach. Multicenter, longitudinal, well-designed studies are strongly encouraged.

1. Introduction

1.1. Purpose

Biomarkers are widely used in translational research as well as in everyday medical practice in different scenarios, including epilepsy. However, so far, a consensus on their definition and application is lacking. The profound and mutually influencing connection between sleep and epilepsy is well known and interests different epileptic syndromes either of pediatric and adult age, as well as other non-epileptic but otherwise dreadful conditions like sudden unexpected death in epilepsy (SUDEP) [1]. In this review, we focus our attention on imaging biomarkers of two entities, namely one epileptic syndrome, sleep-related hypermotor epilepsy (SHE), and one non-epileptic disorder, sudden unexpected death in epilepsy (SUDEP). The rationale behind this choice is twofold: sleep is a common trigger for both conditions to occur. Moreover, while in the last years there was an explosion of imaging research studies, including systematic and not systematic reviews in SUDEP, SHE research lacks similar evidence, likely due to the rarity of the condition, the difficulties to diagnose and the heterogeneity of

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imaging data. Nevertheless, to investigate the relationships between those phenomenon trough imaging biomarkers is not trivial as it could help to clarify the mechanisms by which sleep can behave as a trigger in different conditions.

In the present work, after an introduction on the concept and definition of biomarker, we provided a brief survey of its different declinations in the field of imaging in epilepsy. Then we synthesized available data on SHE and SUDEP imaging biomarkers, always attempting to clarify whether they might be deemed as *diagnostic, prognostic* or with other clinical significance, to encourage the utilization of biomarkers in clinical practice. Finally, we used the information collected to speculate and propose potential imaging biomarkers that can explain the basis of night-time factors facilitating seizures occurrence in both situations.

1.2. Biomarkers: what they are and how to use

In the 2000′, the National Institutes of Health (NIH) defined a biomarker as "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [2]. A more recent and wider definition of biomarker is "a biological observation that substitutes for and ideally predicts a clinically relevant endpoint or intermediate outcome that is more difficult to observe" [3]. Summarizing, a biomarker could be defined as a measurable indicator of some biological state or condition.

Several non-mutually exclusive subtypes of biomarkers have been defined according to their applications: *susceptibility, diagnostic*, *prognostic, predictive, response, monitoring* and *safety* biomarkers (Table 1). Importantly, a single biomarker could meet the criteria for different biomarker's types, depending on how it is used [4]. Finally, the relevance of a specific biomarker is strongly related to the time window of appearance/discovery (Fig. 1). For instance, the same imaging disease hallmark, which plays a pivotal role in the preclinical stage, anticipating the disease onset as *susceptibility* biomarker, may become trivial once the diagnosis is made.

1.3. Biomarkers in epilepsy

Schematically, biomarkers in epilepsy can be classified in two broad categories:

- Biomarkers of *ictogenesis*, linked to the propensity to suffer from an unprovoked seizure.
- Biomarkers of *epileptogenesis*, tied to the development of epilepsy, defined as the growing and the extension of tissue capable of generating spontaneous seizures [5,6].

Table 1
Biomarkers' definitions (adapted from Califf, 2018[4]).

Type of biomarker	Definition
Diagnostic	Confirms the presence of a disease or condition of interest. Largely used in the Classification process
Prognostic	Identifies the likelihood of a clinical event, disease recurrence, or disease progression
Monitoring	Measured serially to assess the status of a disease or medical condition
Predictive	Its level can predict the outcome or the response to a medical product or action
Response	Its level changes in response to exposure to a medical product or an environmental agent
Susceptibility	Indicates the possibility of developing a disease or medical condition in an individual without any manifest sign
Safety	measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of a toxicity as an adverse event.

Within each of these two concepts, all the biomarkers' categories previously described can be applied, resulting in different subcategories.

Biomarkers of SHE, as well as of any type of epilepsy, can be found in a variety of data types, including clinical, electrophysiological, genetic/molecular, and imaging data. While clinical and electrophysiological biomarkers have historically been the most utilized, there is now a growing recognition of two newer categories: genetic/molecular and imaging biomarkers. The same significant interest is also directed towards SUDEP biomarkers. SUDEP is not an epileptic syndrome but a rare and fatal complication common to many forms of epilepsy, occurring mainly during sleep. In this context as well, imaging is increasingly integrated into a multimodal framework where diverse biomarker types, stemming from different approaches and encompassing various systems, are combined to shed light on SUDEP pathophysiology, creating a model to assess patient's risk profile.

1.4. Imaging biomarkers

Once the suspicion of a seizure disorder has been established, neuroimaging is crucial in determining disease etiology, assessing prognosis, and planning appropriate therapeutic options. Therefore, neuroimaging might be seen as the main source of epilepsy biomarkers [7–9]. Additionally, although still not diffusely integrated in the everyday clinical practice, advanced neuroimaging techniques have been developed to guide the identification of subtle structural anomalies in the epileptic brain, which can miss by the naked eye examination. Besides their role in the definition of the seizure-onset zone, these techniques can reveal remote (and frequently overlooked) consequences of the disease on different brain key nodes, elevating the condition to a 'network-level' disorder [10]. However, given the complex evolution of the epileptogenic process, often preceded by a long asymptomatic phase, defining whether these brain anomalies should be considered cause or rather consequences of the disease itself remains one of the most challenging questions.

In patients with MRI-standard detectable lesions, both the presence and the complete surgical resection of the seizure onset zone (SOZ) are considered the most robust *prognostic* indicators of the subsequent outcome [11,12]. The scenario is far more complicated in patients with subtle cortical alterations or in patients presenting with an apparently 'normal' brain MRI. In 2019 a ILAE task force defined a set of recommendations to improve images acquisition protocols [13], additionally endorsing the use of several currently available software for post-processing techniques, able to provide reliable information on patients' anatomy and pathology. Moving from structural imaging, both functional and metabolic techniques might capture different features of the underlying pathological mechanism. Functional MRI imaging (fMRI), based on BOLD (blood oxygen level dependent) signal fluctuations between regions, confirmed the presence of large-scale network alterations in patients with epilepsy, providing several noninvasive biomarkers of epileptogenesis and ictogenesis, especially analyzing connectivity patterns derived from resting state (rs-fMRI) [14–16]. Finally, various non-invasive or minimally invasive metabolic imaging techniques can be employed to assess the functional pathways within brain regions. Radioactive molecules such as 18-F-fluorodeoxyglucose (FDG) have the capacity to distinguish between epileptogenic and non-epileptogenic lesions in various genetic-structural epilepsies [17]. Moreover, they reveal regional impairments extending beyond the presumed epileptogenic lesion [18]. This once again emphasizes that epilepsy is a complex brain condition, suggesting that valuable susceptibility, diagnostic, predictive, and prognostic biomarkers might be rooted in extensive brain networks.

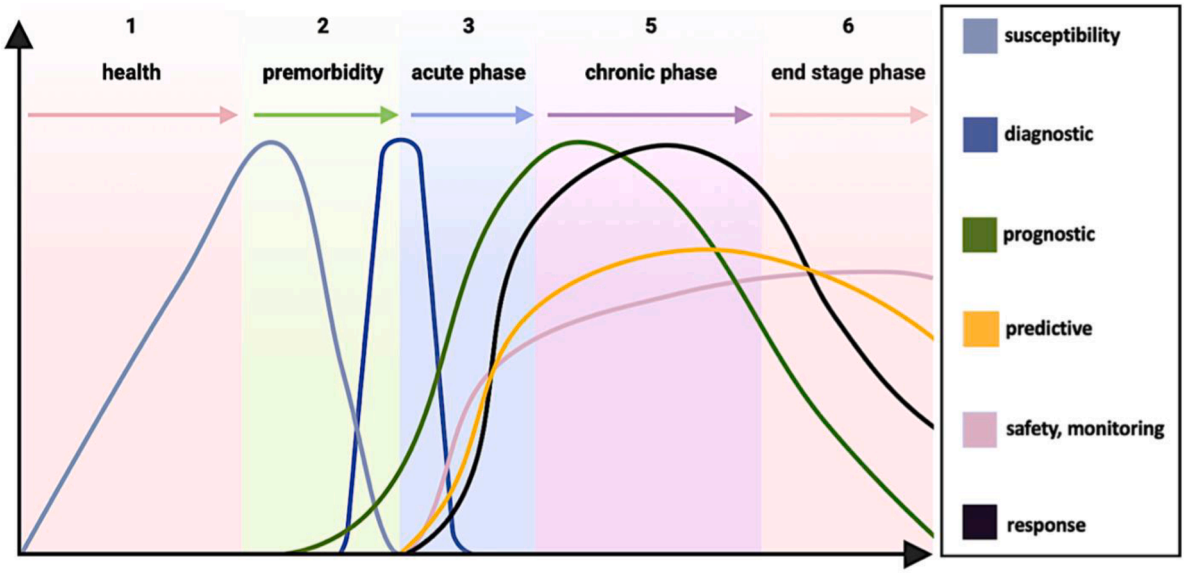

Fig. 1. Schematic representation of the ideal application area for the different biomarker subtypes, according to various stages of a theoretical disease. The vertical axis represents the potential utility value, while the horizontal axis represents time. Progressive numbering in the upper part of the figure represents different disease phases. For example: a biomarker of susceptibility (light blue in the image) is highly informative during health and premorbid stages, while a monitoring biomarker (light pink) is far more useful during advanced disease phases.

2. SHE biomarkers

2.1. Background

SHE is a rare form of focal epilepsy characterized by asymmetric tonic-dystonic posturing and/or hyperkinetic seizures occurring mostly during non-REM (rapid eye movements) sleep and associated to different etiology (genetic, structural and/or acquired) [19]. SHE diagnosis can be challenging, also due to its clinical and electrophysiological similarities with non-REM sleep parasomnias [20]. In this perspective brain imaging could be useful to support SHE diagnosis (*susceptibility* and *diagnostic* biomarkers) and target therapeutic strategies (*prognostic* and *predictive* biomarkers) (Table 2).

2.2. Structural biomarkers

The identification of *diagnostic* biomarkers is particularly relevant for SHE, as electrophysiological data and clinical history might be uninformative or equivocal. The majority of lesional SHE cases might be associated with congenital malformations of cortical development such as focal cortical dysplasia (FCD) or with acquired brain lesions, including low-grade tumors and hippocampal sclerosis [21]. The presence of FCD significantly increases the risk of nocturnal epilepsy independent of the lesion's localization within the cortex *(diagnostic* biomarker*)*, and with higher risk for smaller lesions [21] (*susceptibility* biomarker).

The application of advanced imaging techniques, as tractography with multi shell diffusion-weighted MRI and magnetization transfer imaging (MTI), might help in detecting subtle structural *diagnostic* biomarkers in apparently non-lesional SHE. Tractography indirectly mirrors white matter tracts integrity, and, in combination with other modalities, it can help to diagnose and further localize the SOZ in patients with SHE [22]. As with other forms of focal epilepsy, also SHE has been screened for the presence of more diffuse structural anomalies. In this perspective, magnetization transfer ratio (MTR), a parameter estimated from diffusion weighted images, revealed that patients affected by SHE present a more widespread tissue alteration compared to age-matched healthy subjects, elevating SHE to a network disorder with global brain alterations apparently independent from its focal origin [23]. The exact topography of these brain anomalies, and whether some differences can be seen depending on the underlying SHE etiology is yet to be defined.

2.3. Metabolic biomarkers

So far, the most remarkable results in SHE come from metabolic investigations. Patients affected by SHE show metabolic dysregulation in the fronto-mesial cortical areas, with a pathological decrease of N-acetyl-aspartate (well-known biomarker of axonal density and integrity) especially in the anterior cingulate cortex compared to controls, with severity directly proportional to seizure burden. This finding confirms that SHE patients, regardless SOZ location, might have a common network alteration with a final relay in the frontal lobe, whose dysfunction facilitates ictal hypermotor phenomena during sleep, turning off tonic inhibition on subcortical motor pattern generators [24].

In 2006, Picard and collaborators, using a PET radiotracer for nicotinic Ach receptors (nAChRs), demonstrated a significant increase of nAChRs in several diencephalic regions (epithalamus, ventral mesencephalon, cerebellum) in a group of patients affected by a familiar form of nocturnal epilepsy (autosomal dominant nocturnal frontal lobe epilepsy, ADNFLE) [25] (Fig. 2). In parallel, the authors found a relative decrease of the same receptors in prefrontal cortical regions. They theorized a hyper-activation of the cholinergic brainstem/diencephalic pathway which may, in turn, pathologically stimulate several thalamus nuclei, converting thalamocortical firing into pathological oscillations that might lastly trigger the ictal mechanism. Prefrontal AChRs density decrease could instead reflect regionally neuronal dysfunction causing the loss of cortical inhibition on brainstem central pattern generators, thus enabling the characteristic hypermotor semeiology of this over-activated cholinergic ascending pathway, as suggested by Naldi and collaborators [24]. Notably, nAChRs density does not seem to be caused by seizures, as most patients were not experiencing ictal events at the time of examination [25], being indeed a promising *susceptibility* and *diagnostic* biomarker for SHE to occur. Additionally, the Ach pivotal role in brainstem circuits responsible for sleep arousal may contribute to the primary occurrence of epileptic manifestations during non-REM sleep, and, in vivo evidence of altered Ach pathway might be considered a

Table 2
Case-study and case-control studies investigating imaging biomarkers in SHE.

Author	Imaging technique	Study design	N°	Main findings	Suggested biomarker
Picard 2006	PET with [18F]-F-A-85,380 (nAChR agonist)	Case-control study	8	Significant increase of nAChRs density in several diencephalic regions, relative decrease in prefrontal cortical regions	Susceptibility Diagnostic Predictive
Fedi 2008	PET with [11C]-SCH23390 (D1R agonist)	Case-control study	12	Reduced striatal D1 free receptor concentration	Susceptibility Diagnostic
Naldi 2017	MR proton spectroscopy	Case-control study	19	NAA/Cr ratio reduction in cortical mesial structures, correlating with seizure frequency	Diagnostic
Tchopev 2018	MR tractography with MTI	Case-study	1	Detection of the seizure onset zone incorporating tractography in multimodal study	Diagnostic Predictive
Evangelisti 2018	Rs-fMRI with graph theoretical approach	Case-control study	13	Higher values of thalamic and cortical sensorimotor FC. Absence of a network hub in the caudate nucleus	Susceptibility Diagnostic
Liu 2021	Rs-fMRI	Case-control study	41	Altered FC in precuneus, sensorimotor cortex and supplementary motor area, more severe according to disease duration	Diagnostic Monitoring

predictive therapeutic biomarker of a good response to an Ach-blocker antiseizure drug, such as carbamazepine and related molecules [25–27]. Starting from the hypothesis that activation of presynaptic nicotinic receptors augments the release of dopamine in the striatum and the prefrontal regions, Fedi and colleagues [28] tested the influence of dopaminergic system in the ADNFLE pathogenesis. According to their results, SHE patients presented a significant reduction of striatal dopaminergic 1 (D1) free receptor concentration, due to elevated extracellular dopamine levels or receptor downregulation. Considering the key role of striatal control on thalamic-frontal projections, the reduced dopaminergic inhibition on the excitatory cortical projections, coupled with the cholinergic pathway dysregulation, may contribute to the hypermotor semeiology in SHE, providing another promising metabolic imaging *susceptibility* and *diagnostic* imaging biomarker of SHE [28] (Fig. 2). So far, to the best of our knowledge, most of imaging research focused on ADNFLE. Conversely, non-genetic cases remain largely unexploited, partially due to the wide heterogeneities in SHE etiologies.

2.4. Functional biomarkers

Functional imaging could reveal network dysregulations underpinning SHE development and, potentially, suggesting valuable noninvasive biomarkers of this condition. Graph theory is a mathematical approach allowing to schematize the human brain as a network composed by nodes and edges [29]. The analysis of circuits and connectivity between each hub of the human graph consent to define the 'topology' and properties of every brain area, providing information on their functioning and health. Brain functional network analysis with graph theory approach recently highlighted the absence of a network hub in the caudate nucleus in SHE patients compared to the controls, validating the above-mentioned PET study [25] and confirming its significance as an intriguing diagnostic biomarker [29]. Additionally, patients affected by SHE show higher values of thalamic functional connectivity (FC) compared to controls [29]. In frontal lobe epilepsies different from SHE, thalamic-whole brain FC was found to be similar to healthy controls, thus suggesting that the increase of thalamic FC could be considered as a noninvasive *diagnostic* biomarker of SHE [30]. From a clinical perspective these thalamic pathways' dysregulation might justify the high prevalence of disorders of arousal (DoA) in patients suffering from SHE. Probably, the two disorders share a common pathological cholinergic arousal reaction, as suggested by functional imaging results and by their electrophysiological commonalities at polysomnographic evaluations [31–34]. While the thalamic FC has been proposed as *diagnostic/susceptibility* biomarker for SHE, the altered connectivity profile in precuneus, sensorimotor cortex and supplementary motor area, which are part of the default mode network (DMN), seems to be associated to disease duration (*monitoring* biomarkers?) [35].

2.5. Conclusion

Currently, imaging can yield two primary types of biomarkers in SHE patients. On one side, when considering SHE in conjunction with other drug-resistant focal epilepsies, advanced structural techniques might soon emerge as promising diagnostic biomarkers [22]. Additionally, these techniques could eventually hold value in tailoring a targeted therapeutic (surgical) approach for MRI-negative subjects, thereby also serving as predictive biomarkers. On the other side, keeping in mind the peculiar and distinctive sleep nature of SHE, functional and metabolic techniques might offer innovative biomarkers to unveil its extensive and night-related networks [24,25,28,29,35]. At present, the question of whether these could be regarded as susceptibility or as effect biomarkers remains unresolved. Nevertheless, in the future, these techniques could assist in understanding why focal lesions in different brain regions share a common pathway to nocturnal seizures, eventually providing insights into the distinctions and similarities with non-epileptic sleep phenomena, like parasomnias.

3. Biomarkers of SUDEP

3.1. Background

SUDEP is the most important epilepsy-related cause of death, occurring in up to 6.3 to 9.3/1000 patients with drug-resistant epilepsy [36]. A definite SUDEP is a sudden, unexpected, (un)witnessed, non-traumatic, nondrowning death, occurring usually nocturnally or during sleep [37], in a patient with epilepsy with or without seizures evidence (excluding status epilepticus), in whom postmortem examination does not reveal a cause of death. If criteria are met but an autopsy is not performed, then is called probable SUDEP [38,39].

The link between sleep and SUDEP is tied and complex. Nobili and colleagues showed how the mean percentage of possibly sleep-related SUDEP in studies including more than 10 subjects was 57 %, reaching 95 % in one, while several evidences highlight the role of nocturnal seizures as an independent risk factor for SUDEP [40,41]. Sleep might favor SUDEP events in different ways. It is well-known that sleep stages largely modulate the dynamic interactions between the autonomic and the cardiovascular system. NREM sleep hosts a progressive increase of

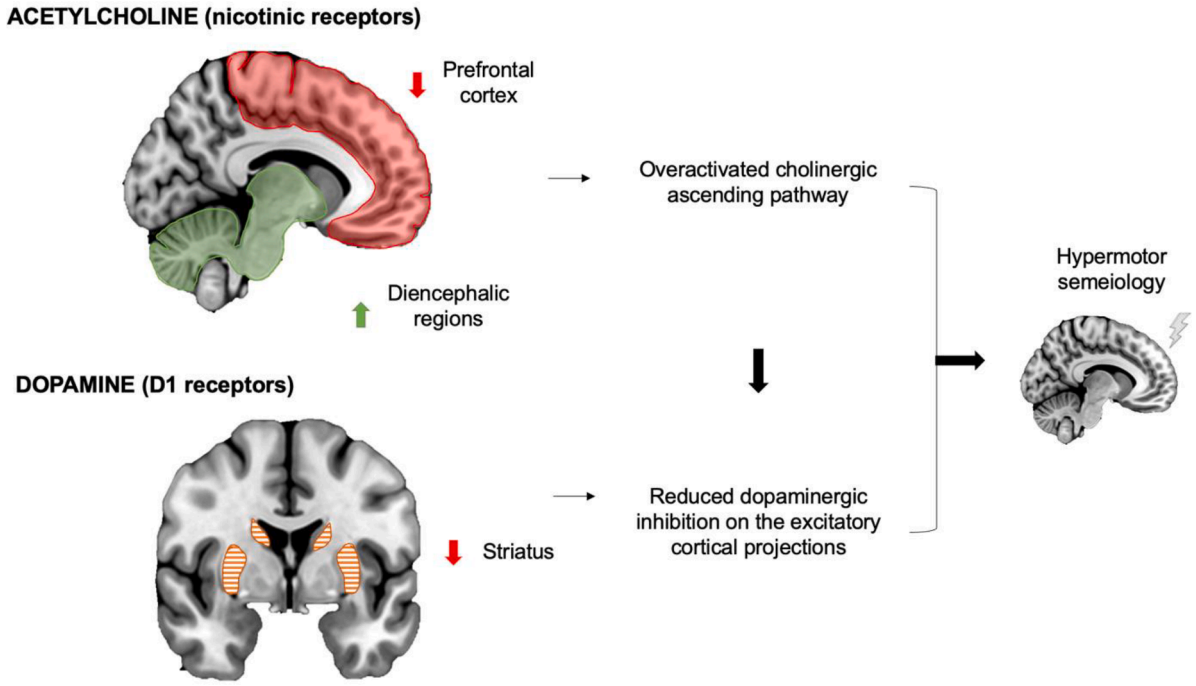

Fig. 2. Schematic representation of cholinergic and dopaminergic anomalies leading to sleep-related hypermotor phenomena in patients affected by SHE. Upper part of the figure: abnormalities in the cholinergic pathway (light red representing hypoactivation and light green indicating hyperactivation); lower part of the figure: abnormalities in the dopaminergic pathway (orange striped areas).

the parasympathetic activity, leading to a reduction in blood pressure and heart rate, while REM sleep is commonly associated with reinforcement of the sympathetic vasomotor tone and bursts in the vagus nerve activation, which can cause cardiac pauses or even brief periods of asystole. REM sleep is also commonly associated with respiratory instability that can favor pathological respiratory events, especially in subjects affected by pre-existing cardiological or pulmonary diseases [42]. By counterpart, NREM sleep might favor occurrence of paroxysmal events through its cyclic oscillatory activities, mirrored by the cyclic alternating pattern (CAP), which behaves as a permissive framework for seizures onset [43,44]. Although numerous deaths for SUDEP had been considered consequences of nocturnal seizures, more recently other circadian factors have been implicated in the SUDEP rhythmicity [45]. Being SUDEP by its nature an unpredictable event, research has focused to identify potential biomarkers of *susceptibility* able to define people at high risk. With recent advances in our understanding of SUDEP pathophysiology [46,47] attention has focused on electrophysiological and imaging biomarkers of impaired cardiorespiratory and autonomic pathways, attempting to determine whether they could be used as valuable *susceptibility* biomarkers [48] (Table 3).

Table 3
Case-control studies evaluating imaging biomarkers in SUDEP and high-risk SUDEP cases.

Author	Imaging technique	Study design	N°	Main findings	Suggested biomarker
Mueller 2014	VBM MRI with graph analysis	Case-control study	2 SUDEP	Dorsal mesencephalic atrophy extending over dorsal pons and upper medulla oblongata. Structural connectivity graph analysis abnormalities	Susceptibility
Tang 2014	Rs-fMRI	Case-control study	0 SUDEP 13 high-risk	Reduced FC in bilateral anterior cingulate cortex and thalami, pons and midbrain	Susceptibility
Wandschneider 2015	VBM MRI	Case-control study	12 SUDEP 34 high-risk	Bilateral thinning of posterior thalami, increased grey matter volume in the right hippocampus, parahippocampal gyrus and amygdala	Susceptibility
Allen 2017	Rs-fMRI	Case-control study	0 SUDEP 14 high-risk	Reduced FC in thalamus, brainstem anterior cingulate cortex, putamen and amygdala. Enhanced FC involving connections to limbic structures from the frontal medio-orbital cortex	Susceptibility
Mueller 2018	Deformation-based morphometry MRI with graph analysis	Case-control study	26 SUDEP.	Widespread brainstem atrophy, with more extensive damage correlating with shorter survival	Susceptibility Prognostic
Allen 2019	Rs-fMRI	Case-control study	8 SUDEP 16 high-risk	Reduced modularity and increased nodal participation between brain regions involved in cardiovascular and breathing control	Susceptibility
Allen 2019	VBM MRI	Case-control study	25 SUDEP 25 high-risk	Thinning of posterior cingulate and thalamus, periaqueductal gray and cerebellum. Increased grey matter volume in entorhinal cortex, parahippocampal gyrus, subcallosal cortex and amygdala	Susceptibility
Whatley 2021	PET with 18-FDG	Case-control study	0 SUDEP 56 high-risk	Increased metabolism in basal ganglia, thalamus, ventral diencephalon, midbrain, pons, and deep cerebellar nuclei	Susceptibility

3.2. Structural biomarkers

Several voxel-based morphometry (VBM) studies revealed volume differences in key cardiorespiratory and autonomic regulatory brain structures (Fig. 3). Wandschneider and colleagues [49], considering both SUDEP cases and high-risk epileptic patients, according to a validated risk factor analysis scores [50], identified bilateral thinning of posterior thalami (pulvinar) and increased grey matter volume in the right hippocampus, parahippocampal gyrus and amygdala. Reduced pulvinar volume, further confirmed in a larger cohort [51], is of particular interest, considering its role in mediating breathing responses in hypoxic situations, as normally happens during ictal episodes [52]. Conversely, the lateralized increased volume of limbic circuitry modulating autonomic functions [49], may be either causes or consequences (e.g., gliosis) of repetitive seizures [53]. In both cases the volumetric data could reflect an underlying chronic autonomic dysregulation which may reflect the inability to recover breathing from hypoxic challenge, ultimately contributing to an increased potential for a fatal outcome (*susceptibility* biomarker). A recent work by Allen [51] revealed the involvement of other cortical and subcortical brain regions structurally impaired in SUDEP, such as cerebellum and posterior cingulate cortex, which appear smaller/thinner compared to high-risk patients and healthy controls. SUDEP patients may present major bilateral cerebellar volume loss [51], perhaps indicating an impaired cerebellar capability to recover from compromised cardiovascular and breathing circumstances [54].

The brainstem, with its important role in cardiorespiratory and arousal control, represents another widely investigated possible structural *susceptibility* biomarker of SUDEP [55,56]. Compared to controls and patients with temporal lobe epilepsy (TLE), two subjects who later died for SUDEP showed severe and widespread dorsal mesencephalic atrophy, extending over dorsal pons and upper medulla oblongata, together with structural connectivity abnormalities in the same areas [57]. Notably, the most severely affected regions involve periaqueductal gray and cuneiform nucleus, structures deeply implicated in networks regulating the autonomic control on cardio-respiratory functions and whose impaired behavior might cause the critical peri- and post-ictal autonomic disturbances eventually ending in SUDEP. Moreover, patients suffering from focal epilepsy who then experienced probable/definite SUDEP have shown to have a more widespread brainstem volume loss compared to those without subsequent SUDEP, with more extensive damage correlated with a shorter survival time [58] (*prognostic* biomarker). These structural brainstem dysfunctions, further confirmed by post-mortem studies [59], might cause not only cardiac arrhythmias and respiratory impairment, but also longer and more often generalized seizures with prolonged impairment of consciousness. Brainstem atrophy and degeneration can be therefore considered both a promising imaging *risk/susceptibility* biomarker and its measurement seems critical to understand the sequence of events leading to SUDEP.

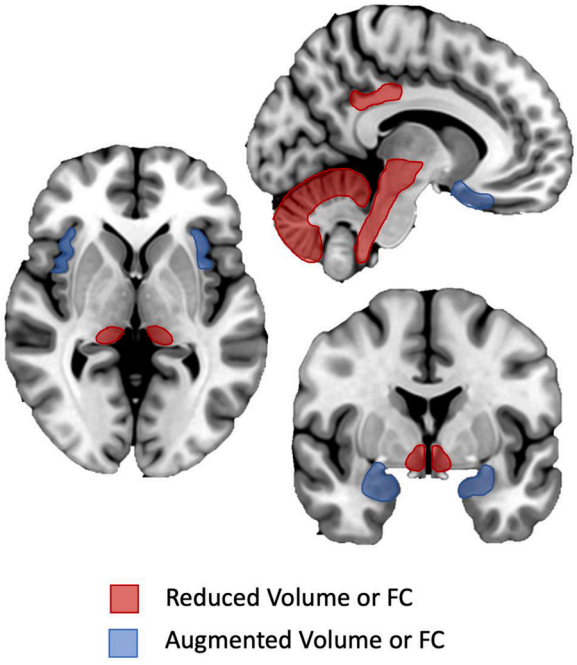

Fig. 3. Simplified three-dimensional snapshot highlighting main compromised brain areas in patients died for SUDEP (studies considering only high-risk patients were not considered). Light red color highlights brain structures with reduced volume and/or FC decrease, including posterior cingulate, bilateral pulvinar, (dorsal) brainstem with periaqueductal gray and cerebellum. Light blue color highlights brain structures with augmented volume and/or increased FC, including insular and orbitofrontal cortex, bilateral hippocampi, parahippocampal gyri and amygdalae. FC: functional connectivity.

3.3. Metabolic imaging biomarkers

Only few studies explored the role of metabolic images to find valuable biomarker of SUDEP, and only one enrolled patients later died for SUDEP [60]. According to their results, high risk SUDEP patients present increased metabolism in regions (basal ganglia, thalamus, ventral diencephalon, midbrain, pons, and deep cerebellar nuclei) involved in cardiovascular, breathing, and autonomic regulation [61] and decrease metabolism over the medial and inferior frontal cortex bilaterally, including the anterior cingulate [60]. Both studies [60,61] although reporting with different results, highlighted the involvement of structures that regulate the cardio-vascular and respiratory functions. Considering that the same structures result structurally and functionally (see below) abnormal in high risk and SUDEP patients [62,63], these abnormalities could represent a promising *risk* biomarker of SUDEP.

3.4. Functional biomarkers

Different rs-fMRI studies in TLE patients at high-risk of SUDEP found reduced FC in several regions, including cingulate cortex, thalamus and brainstem [62,63] (Fig. 3). Notably, an enhanced FC emerged in high-risk SUDEP patients between limbic structures and frontal medio-orbital cortex [63]. The frontal enhanced connectivity could reflect an imbalance in the medial prefrontal–hippocampal circuitry involved in autonomic-modulated blood pressure regulation [64]. Graph theory results [65] showed how SUDEP (and high-risk) subjects presented a reduced modularity, a measure indicating the level of brain networks organization, between critical brain regions involved in cardiovascular and breathing control. Furthermore, they also presented increased nodal participation (a measure of the degree to which a brain region communicates with other modules) in the same structures, including thalamus and insula, enhancing excessive neuronal interactions among these vital structures [65]. Finally, a very recent rs-fMRI study found out a negative correlation between the strength of anterior insula connectivity and the interval between fMRI scan and time of SUDEP. Dysfunctional insular connectivity may thus play a pivotal role in SUDEP, and its measure might be considered a valuable noninvasive *predictive* biomarker of SUDEP risk [66].

3.5. Conclusion

In SUDEP patients, sleep might play a crucial role in triggering several multi-domain risk factors ultimately ending with death [40]. Cortical activity, especially in the limbic circuits, had been proved to directly modulate the autonomic tone in humans [67]. The continuous fluctuations of the autonomic nervous system with sleep stages and the physiologic oscillations within NREM sleep might directly impact on the cardiorespiratory system in high-risk SUDEP patients, increasing their

risk for nocturnal fatal events. SUDEP is typically considered as a storm that strikes without warning signals [65]. Nevertheless, objective and even relatively precocious subtle structural and functional substrates alterations, biomarkers of an underlying intrinsic vulnerability, are present in patients eventually experiencing SUDEP. For instance, post GTCS hypoperfusion in brainstem respiratory centers [68], could have both acute and chronic effects, causing network dysfunctions in brain regions regulating cardiorespiratory functions and ultimately becoming fatal when superimposing on structurally and functionally chronic impaired structures. In this scenario, imaging alterations could be as both *susceptibility* biomarkers (risk biomarker) of SUDEP and *diagnostic* biomarkers (biomarkers of *effect*) of an underlying pathological ongoing loop ultimately ending with SUDEP. Knowing these abnormalities would implement our understanding in brain dysfunction in SUDEP, letting us to promote innovative studies and ultimately to develop valid therapeutic and preventive strategies. In this puzzling landscape, where most data originate from patients classified as high risk for SUDEP rather than from individuals who have experienced SUDEP, another enlightening piece might emerge through neuropathology. Recently, an ex vivo high-resolution MRI study provided evidence of volume alterations in autonomic and respiratory regulatory regions in SUDEP [69]. Additionally, emerging pathological data highlight the presence of regionally selective molecular alterations in neuronal populations within brainstem nuclei in patients who died of SUDEP [70]. Taken together, these findings underscore the importance of in vivo structural and metabolic alterations in the same structures as promising and targeted biomarkers *risk* SUDEP biomarkers.

4. Conclusion and future directions

In the field of research of epileptogenic biomarkers, SUDEP and SHE represent a real challenge. Indeed, while it is possible to seek and validate valuable imaging biomarkers for several other epileptic entities through prospective multicenter studies, it is not an easy task for these rare phenomena.

As a matter of fact, most evidence on the topic are derived from small single center experiences with scarcely comparable results, due to substantial technical discrepancies, hampering the possibility to perform any metanalytic approach of results. Among others, advanced post-processing techniques are perhaps the most promising tool in identifying valid biomarkers. However, in the absence of methodological homogeneity, the chance to obtain replicable data remain elusive. Given the complexity of the epileptogenic process, it would be even more interesting to match data collected from different methodologies such as structural, functional and metabolic brain imaging with electrophysiological and genetic-molecular studies, building a multimodal framework able to assess the dynamic of the disease in a holistic perspective.

Moreover, gaining a deeper understanding of the underlying reason for the nocturnal occurrence of SHE could aid us in comprehending the basis of night-time factors facilitating SUDEP occurrence. For instance, the altered arousal mechanism underlying SHE clinical manifestations, due to brainstem cholinergic and dopaminergic dysregulation highlighted in metabolic imaging studies [24,25,28], could be somehow related to the widespread and progressive atrophy of the same structures identified as potential biomarkers for SUDEP in various structural imaging studies[51–53]. Within this framework, it is worth noting that not only SHE but also all other epileptic conditions displaying a notable propensity for nocturnal events should be considered.

Authors contribution statement

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

CRediT authorship contribution statement

Francesco Misirocchi: Conceptualization, Writing – review & editing, Writing – original draft. **Anna Elisabetta Vaudano:** Writing – review & editing. **Irene Florindo:** Writing – review & editing, Writing – original draft. **Lucia Zinno:** Writing – review & editing. **Alessandro Zilioli:** Writing – review & editing. **Elisa Mannini:** Writing – review & editing, Writing – original draft. **Liborio Parrino:** Writing – review & editing. **Carlotta Mutti:** Conceptualization, Writing – review & editing, Writing – original draft.

Declaration of competing interest

A.E. Vaudano received personal compensation as scientific advisory board member for Angelini Pharma. None of other authors reported disclosures relevant financial or other conflicts of interest.

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None

References

[1] Nobili L, Frauscher B, Eriksson S, Gibbs SA, Halasz P, Lambert I, Manni R, Peter-Derex L, Proserpio P, Provini F, de Weerd A, Parrino L. Sleep and epilepsy: a snapshot of knowledge and future research lines. J Sleep Res 2022;31(4):e13622. https://doi.org/10.1111/jsr.13622. Epub 2022 Apr 29. PMID: 35487880; PMCID: PMC9540671.

[2] NIH Definitions Working Group. Biomarkers and surrogate endpoints in clinical research: definitions and conceptual model. In: Downing GJ, editor. Biomarkers and surrogate endpoints. Amsterdam: Elsevier; 2000. p. 1–9.

[3] Aronson JK, Ferner RE. Biomarkers-A general review. Curr Protoc Pharmacol 2017; 76(9). https://doi.org/10.1002/cpph.19. 23.1-9.23.17.

[4] Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood) 2018;243(3):213–21. https://doi.org/10.1177/1535370217750088.

[5] Engel Jr J, Pitkänen A, Loeb JA, et al. Epilepsy biomarkers. Epilepsia 2013;54 (Suppl 4):61–9. https://doi.org/10.1111/epi.12299.

[6] Pitkänen A, Löscher W, Vezzani A, Becker AJ, Simonato M, Lukasiuk K, Gröhn O, Bankstahl JP, Friedman A, Aronica E, Gorter JA, Ravizza T, Sisodiya SM, Kokaia M, Beck H. Advances in the development of biomarkers for epilepsy. Lancet Neurol 2016;15(8):843–56. https://doi.org/10.1016/S1474-4422(16)00112-5. PMID: 27302363.

[7] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel Jr J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–82. https://doi.org/10.1111/epi.12550. Epub 2014 Apr 14. PMID: 24730690.

[8] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58(4):512–21. https://doi.org/10.1111/epi.13709. Epub 2017 Mar 8. PMID: 28276062; PMCID: PMC5386840.

[9] Bernasconi A, Bernasconi N. Unveiling epileptogenic lesions: the contribution of image processing. Epilepsia 2011;52(Suppl 4):20–4. https://doi.org/10.1111/j.1528-1167.2011.03146.x. PMID: 21732936.

[10] Royer J, Bernhardt BC, Larivière S, Gleichgerrcht E, Vorderwülbecke BJ, Vulliémoz S, Bonilha L. Epilepsy and brain network hubs. Epilepsia 2022;63(3): 537–50. https://doi.org/10.1111/epi.17171. PMID: 35092011.

[11] Téllez-Zenteno JF, Hernández Ronguillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89:310–8. PMID: 20227852.

[12] Krsek P, Maton B, Jayakar P, Dean P, Korman B, Rey G, Dunoyer C, Pacheco-Jacome E, Morrison G, Ragheb J, Vinters HV, Resnick T, Duchowny M. Incomplete resection of focal cortical dysplasia is the main predictor of poor postsurgical outcome. Neurology 2009;72(3):217–23. https://doi.org/10.1212/01.wnl.0000334365.22854.d3. PMID: 19005171.

[13] Bernasconi A, Cendes F, Theodore WH, Gill RS, Koepp MJ, Hogan RE, Jackson GD, Federico P, Labate A, Vaudano AE, Blümcke I, Ryvlin P, Bernasconi N. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia 2019;60(6):1054–68. https://doi.org/10.1111/epi.15612. PMID: 31077478.

[14] Foit NA, Bernasconi A, Bernasconi N. Functional networks in epilepsy presurgical evaluation. Neurosurg Clin N Am 2020;31(4):573–82. https://doi.org/10.1016/j.nec.2020.03.004.

[15] Audrain S, Barnett AJ, McAndrews MP. Language network measures at rest indicate individual differences in naming decline after anterior temporal lobe

resection. Hum Brain Mapp 2018;39(11):4404–19. https://doi.org/10.1002/hbm.24281. PMID: 29956405; PMCID: PMC6866601.
[16] Xu Q, Zhang Z, Liao W, Xiang L, Yang F, Wang Z, Chen G, Tan Q, Jiao Q, Lu G. Time-shift homotopic connectivity in mesial temporal lobe epilepsy. AJNR Am J Neuroradiol 2014;35(9):1746–52. https://doi.org/10.3174/ajnr.A3934. PMID: 24742802; PMCID: PMC7966270.
[17] Kumar A, Asano E, Chugani HT. α-[^{11}C]-methyl-L-tryptophan PET for tracer localization of epileptogenic brain regions: clinical studies. Biomark Med 2011;5(5):577–84. https://doi.org/10.2217/bmm.11.68. PMID: 22003906; PMCID: PMC3226729.
[18] Barros DA, Pressler RM, Luthra S, Jones PA, Trigg W, Micallef C, Symms MR, Brooks DJ, Duncan JS. NMDA receptor binding in focal epilepsies. J Neurol Neurosurg Psychiatry 2015;86(10):1150–7. https://doi.org/10.1136/jnnp-2014-309897. PMID: 25991402; PMCID: PMC4602274.
[19] Tinuper P, Bisulli F, Cross JH, Hesdorffer D, Kahane P, Nobili L, Provini F, Scheffer IE, Tassi L, Vignatelli L, Bassetti C, Cirignotta F, Derry C, Gambardella A, Guerrini R, Halasz P, Licchetta L, Mahowald M, Manni R, Marini C, Mostacci B, Naldi I, Parrino L, Picard F, Pugliatti M, Ryvlin P, Vigevano F, Zucconi M, Berkovic S, Ottman R. Definition and diagnostic criteria of sleep-related hypermotor epilepsy. Neurology 2016;87(20). https://doi.org/10.1212/WNL.0000000000003292. Supplement_2-S20-S28PMID: 27856772.
[20] Halász P, Szűcs A, Mutti C, Parrino L. Disorders of arousal and sleep-related hypermotor epilepsy - overview and challenges night is a battlefield of sleep and arousal promoting forces. Neurol Sci 2022;43(2):927–37. https://doi.org/10.1007/s10072-021-05857-0. Epub 2022 Jan 5. PMID: 34984571.
[21] Wang Y, He C, Chen C, Wang Z, Ming W, Qiu J, Ying M, Chen W, Jin B, Li H, Ding M, Wang S. Focal cortical dysplasia links to sleep-related epilepsy in symptomatic focal epilepsy. Epilepsy Behav 2022;127:108507. https://doi.org/10.1016/j.yebeh.2021.108507. Epub 2021 Dec 27. PMID: 34968776.
[22] Tchopev ZN, Yeh PH, Morgan GW, Meyer E, Wolf JM, Ollinger JM, Riedy GP, Young LC. Acquired sleep-related hypermotor epilepsy with disrupted white matter tracts assessed by multishell diffusion magnetic resonance imaging. Front Neurol 2018;9:6. https://doi.org/10.3389/fneur.2018.00006. PMID: 29403431; PMCID: PMC5786569.
[23] Ferini-Strambi L, Bozzali M, Cercignani M, Oldani A, Zucconi M, Filippi M. Magnetization transfer and diffusion-weighted imaging in nocturnal frontal lobe epilepsy. Neurology 2000;54(12):2331–3. https://doi.org/10.1212/wnl.54.12.2331. PMID: 10881265.
[24] Naldi I, Bisulli F, Testa C, Rizzo G, Ferri L, Gramegna LL, Licchetta L, Lodi R, Tonon C, Tinuper P. Proton MR spectroscopy in patients with Sleep-Related Hypermotor Epilepsy (SHE): evidence of altered cingulate cortex metabolism. Sleep. 2017;40(9):zsx115.
[25] Picard F, Bruel D, Servent D, Saba W, Fruchart-Gaillard C, Schöllhorn-Peyronneau MA, Dourmap N, Krebs MO, Placet M, Bourgeois M, Brückert E. Alteration of the in vivo nicotinic receptor density in ADNFLE patients: a PET study. Brain 2006;129(Pt 8):2047–60.
[26] Tassinari CA, Gardella E, Meletti S, Rubboli G. The neuroethological interpretation of motor behaviours in 'nocturnal-hyperkinetic-frontal seizures': emergence of 'innate' motor behaviours and role of central pattern generators. In: Beaumanoir A, Andermann F, Chauvel P, Mira L, Zifkin B, editors. Frontal lobe seizures and epilepsies in children. Montrouge: John Libbey Eurotext; 2003. p. 43–8.
[27] Di Resta C, Ambrosi P, Curia G, Becchetti A. Effect of carbamazepine and oxcarbazepine on wild-type and mutant neuronal nicotinic acetylcholine receptors linked to nocturnal frontal lobe epilepsy. Eur J Pharmacol 2010;643(1):13–20. Sep 15.
[28] Fedi M, Berkovic SF, Scheffer IE, O'Keefe G, Marini C, Mulligan R, Mulley JC, Roncaroli F, Binelli S, Malacarne M, Tinuper P. Reduced striatal D1 receptor binding in autosomal dominant nocturnal frontal lobe epilepsy. Neurology 2008;71(6):795–8.
[29] Evangelisti S, Testa C, Ferri L, Gramegna LL, Manners DN, Rizzo G, Remondini D, Castellani G, Naldi I, Bisulli F, Tonon C, Tinuper P, Lodi R. Brain functional connectivity in sleep-related hypermotor epilepsy. NeuroImage 2017;15:95–101. Jul 12.
[30] Dong L, Wang P, Peng R, Jiang S, Klugah-Brown B, Luo C, Yao D. Altered basal ganglia-cortical functional connections in frontal lobe epilepsy: a resting-state fMRI study. Epilepsy Res 2016;128:12–20.
[31] 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. Sep 1.
[32] Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev 2006;10:267–85.
[33] Mutti C, Bernabè G, Barozzi N, Ciliento R, Trippi I, Pedrazzi G, Azzi N, Parrino L. Commonalities and differences in NREM parasomnias and sleep-related epilepsy: is there a continuum between the two conditions? Front Neurol 2020;11:569.
[34] Halász P, Szűcs A. Sleep and epilepsy link by plasticity. Front Neurol 2020;11:911.
[35] Liu W, Yue Q, Wu X, Gong Q, Zhou D. Abnormal blood oxygen level-dependent fluctuations and remote connectivity in sleep-related hypermotor epilepsy. Acta Neurol Scand 2021;143(5):514–20.
[36] Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998;51(5):1270–4.
[37] Sveinsson O, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: a nationwide population-based case series. Epilepsia 2018;59(5):1074–82.
[38] Annegers JF. United States perspective on definitions and classifications. Epilepsia 1997;38(11 Suppl):S9–12.
[39] Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53(2):227–33.
[40] Nobili L, Proserpio P, Rubboli G, Montano N, Didato G, Tassinari CA. Sudden unexpected death in epilepsy (SUDEP) and sleep. Sleep Medicine Rev 2011;15(4):237–46.
[41] Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sanders JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012;53(2):253–7.
[42] Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7.
[43] Neurophysiol. 2000;111 Suppl 2:S39–46. doi: 10.1016/s1388-2457(00)00400-4. PMID: 10996553.
[44] Rocamora R, Andrzejak RG, Jiménez-Conde J, Elger CE. Sleep modulation of epileptic activity in mesial and neocortical temporal lobe epilepsy: a study with depth and subdural electrodes. Epilepsy Behav 2013;28(2):185–90. https://doi.org/10.1016/j.yebeh.2013.04.010. Epub 2013 Jun 10. PMID: 23751358.
[45] Kreitlow BL, Li W, Buchanan GF. Chronobiology of epilepsy and sudden unexpected death in epilepsy. Front Neurosci 2022;16:936104.
[46] Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTE-MUS): a retrospective study. Lancet Neurol 2013;12(10):966–77. https://doi.org/10.1016/S1474-4422(13)70156-5. PMID: 24050797.
[47] Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015;84(7):703–9. https://doi.org/10.1212/WNL.0000000000001281. Epub 2015 Jan 21. PMID: 25609761; PMCID: PMC4335992.
[48] DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: risk factors, biomarkers, and prevention. Acta Neurol Scand 2019;139(3):220–30. https://doi.org/10.1111/ane.13049. Epub 2018 Dec 11. PMID: 30443951.
[49] Wandschneider B, Koepp M, Scott C, Micallef C, Balestrini S, Sisodiya SM, Thom M, Harper RM, Sander JW, Vos SB, Duncan JS, Lhatoo S, Diehl B. Structural imaging biomarkers of sudden unexpected death in epilepsy. Brain 2015;138(Pt 10):2907–19. https://doi.org/10.1093/brain/awv233. Epub 2015 Aug 10. PMID: 26264515; PMCID: PMC4671481.
[50] Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52(6):1150–9. https://doi.org/10.1111/j.1528-1167.2011.03020.x. Epub 2011 Apr 15. PMID: 21488937.
[51] Allen LA, Vos SB, Kumar R, Ogren JA, Harper RK, Harper RM, et al. Cerebellar, limbic and midbrain volume alterations in sudden unexpected death in epilepsy (SUDEP). Epilepsia 2019;60(4):781–91. https://doi.org/10.1111/epi.14685.
[52] Harper RM, Macey PM, Woo MA, Macey KE, Keens TG, Gozal D, et al. Hypercapnic exposure in congenital central hypoventilation syndrome reveals central nervous system respiratory control mechanisms. J Neurophysiol 2005;93(3):1647–58. https://doi.org/10.1152/jn.00863.2004.
[53] Yasuda CL, Betting LE, Cendes F. Voxel-based morphometry and epilepsy [Review]. Expert Rev Neurother 2010;10(6):975–84. https://doi.org/10.1586/ern.10.59.
[54] Xu F, Frazier DT. Role of the cerebellar deep nuclei in respiratory modulation. Cerebellum 2002;1(1):35–40. https://doi.org/10.1080/147342202753419143.
[55] Zhang H, Zhao H, Zeng C, Van Dort C, Fangold CL, Taylor NE, et al. Optogenetic activation of 5-HT neurons in the dorsal raphe suppresses seizure-induced respiratory arrest and produces anticonvulsant effect in the DBA/1 mouse SUDEP model. Neurobiol Dis 2018;110:47–58. https://doi.org/10.1016/j.nbd.2017.10.018.
[56] Dampney RA. Central mechanisms regulating coordinated cardiovascular and respiratory function during stress and arousal. Am J Physiol Regul Integr Comp Physiol 2015;309(5):R429–43. https://doi.org/10.1152/ajpregu.00053.2015.
[57] Mueller SG, Bateman LM, Laxer KD. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. Neuroimage Clin 2014;5:208–16. https://doi.org/10.1016/j.nicl.2014.05.007.
[58] Mueller SG, Nei M, Bateman LM, Knowlton R, Laxer KD, Friedman D, et al. Brainstem network disruption: a pathway to sudden unexplained death in epilepsy? Hum Brain Mapp 2018;39(12):4820–30. https://doi.org/10.1002/hbm.24325.
[59] Patodia S, Tachrount M, Somani A, Scheffer I, Yousry T, Golay X, Sisodiya SM, Thom M. MRI and pathology correlations in the medulla in sudden unexpected death in epilepsy (SUDEP): a postmortem study. Neuropathol Appl Neurobiol 2021;47(1):157–70. https://doi.org/10.1111/nan.12638. Epub 2020 Jul 15PMID: 32559314; PMCID: PMC7749076.
[60] Kumar A, Alhourani H, Abdelkader A, Shah AK, Juhász C, Basha MM. Frontal lobe hypometabolism associated with Sudden Unexpected Death in Epilepsy (SUDEP) risk: an objective PET study. Epilepsy Behav 2021;122:108185. https://doi.org/10.1016/j.yebeh.2021.108185. Epub 2021 Jul 9. PMID: 34252829.
[61] Whatley BP, Winston JS, Allen LA, Vos SB, Jha A, Scott CA, Smith AL, Chowdhury FA, Bomanji JB, Lhatoo SD, Harper RM, Diehl B. Distinct patterns of brain metabolism in patients at risk of sudden unexpected death in epilepsy. Front Neurol 2021;12:623358. https://doi.org/10.3389/fneur.2021.623358. PMID: 34899550; PMCID: PMC8651549.
[62] Tang Y, Chen Q, Yu X, Xia W, Luo C, Huang X, Tang H, Gong Q, Zhou D. A resting-state functional connectivity study in patients at high risk for sudden unexpected death in epilepsy. Epilepsy Behav 2014;41:33–8. https://doi.org/10.1016/j.yebeh.2014.08.140. Epub 2014 Sep 29. PMID: 25277976.
[63] Allen LA, Harper RM, Kumar R, Guye M, Ogren JA, Lhatoo SD, Lemieux L, Scott CA, Vos SB, Rani S, Diehl B. Dysfunctional brain networking among autonomic regulatory structures in temporal lobe epilepsy patients at high risk of

sudden unexpected death in epilepsy. Front Neurol 2017;8:544. https://doi.org/10.3389/fneur.2017.00544. PMID: 29085330; PMCID: PMC5650686.

[64] Harper RM, Bandler R, Spriggs D, Alger JR. Lateralized and widespread brain activation during transient blood pressure elevation revealed by magnetic resonance imaging. J Comp Neurol 2000;417(2):195–204. https://doi.org/10.1002/(sici)1096-9861(20000207)417:2<195::aid-cne5>3.0.co;2-v. Feb 7PMID: 10660897.

[65] Allen LA, Harper RM, Guye M, Kumar R, Ogren JA, Lhatoo SD, Vos SB, Scott CA, Lemieux L, Diehl B. Altered brain connectivity in sudden unexpected death in epilepsy (SUDEP) revealed using resting-state fMRI. Neuroimage Clin 2019;24:102060. https://doi.org/10.1016/j.nicl.2019.102060. Epub 2019 Oct 28. PMID: 31722289; PMCID: PMC6849487.

[66] Kassinopoulos, M., Rolandi, N., Alphan, L., Harper, R.M., Oliveira, J., Scott, C., Kozák, L.R., Guye, M., Lemieux, L., & Diehl, B. (2023). Brain Connectivity Correlates of Breathing and Cardiac Irregularities in SUDEP: a Resting-State fMRI Study. bioRxiv: the preprint server for biology, 2023.05.19.541412. https://doi.org/10.1101/2023.05.19.541412.

[67] Alasfour A, Jiang X, Gonzalez-Martinez J, Gilja V, Halgren E. High γ activity in cortex and hippocampus is correlated with autonomic tone during sleep. eNeuro 2021;8(6). https://doi.org/10.1523/ENEURO.0194-21.2021. ENEURO.0194-21.2021PMID: 34732536; PMCID: PMC8607912.

[68] Liu J, Peedicail JS, Gaxiola-Valdez I, Li E, Mosher V, Wilson W, Perera T, Singh S, Teskey GC, P; Federico. Calgary comprehensive epilepsy program collaborators. Postictal brainstem hypoperfusion and risk factors for sudden unexpected death in epilepsy. Neurology 2020;95(12):e1694–705. https://doi.org/10.1212/WNL.0000000000010360. Epub 2020 Jul 16PMID: 32675079; PMCID: PMC7713728.

[69] Patodia S, Tachrount M, Somani A, Scheffer I, Yousry T, Golay X, Sisodiya SM, Thom M. MRI and pathology correlations in the medulla in sudden unexpected death in epilepsy (SUDEP): a postmortem study. Neuropathol Appl Neurobiol 2021;47(1):157–70. https://doi.org/10.1111/nan.12638. PMID: 32559314; PMCID: PMC7749076.

[70] Patodia S, Somani A, O'Hare M, Venkateswaran R, Liu J, Michalak Z, Ellis M, Scheffer IE, Diehl B, Sisodiya SM, Thom M. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. Brain 2018;141(6):1719–33. https://doi.org/10.1093/brain/awy078. PMID: 29608654; PMCID: PMC5972615.