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Review

Disorders of arousal and sleep-related hypermotor epilepsy are interrelated. Some new viewpoints

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ABSTRACT

NREM parasomnias overlap with sleep-related hypermotor epilepsies in multiple ways. Both conditions are characterized by fragmented sleep; share symptomatic features; have family-, and population-genetic relationships; and NREM parasomnia-episodes are underlain by sleep-wake dissociation likely featuring SHE seizures as well. Most importantly, the two conditions have very similar links with NREM sleep's high homeostatic pressure periods closely related to sleep microstructure including sleep-like micro-arousals, the dynamics of cyclic alternating pattern A1 and slow wave bistability. While the unquestionable distinction of the two conditions, epileptic and non-epileptic, is essential both theoretically and practically; their striking relationship calls for explanation.

1. Introduction

First Broughton [1] described the spectrum of arousal parasomnias (termed also disorders of arousal; DOA) in the sixties of the last century. Nearly twenty years later, Lugaresi [2] set down the term „nocturnal paroxysmal dystonia" (a parasomnia) that was renamed to 'nocturnal frontal lobe epilepsy'; and this denomination has been changed again in 2014 by an international consensus conference to 'sleep related hypermotor epilepsy (SHE)' [3]. Since then, the literature has accepted DOA and SHE as different entities; a sleep disorder and an epilepsy.

However, the overlaps of DOA and SHE have been revealed in the literature again [4–6], and a recent paper pointed out the weakness of arguments supporting the epileptic nature - interictal and ictal EEG signs - of SHE [7].

Due to the clinical similarity of the two syndromes, differentiating them may be challenging in clinical practice [7,8]. Therefore, the recent literature is dominated by search for discriminatory features and efforts to find delineating tools e.g. scores and questionnaires.

In this review we aim to compare SHE and DOA, and reinterpret related phenomena; hoping that some new lines for further research can be proposed.

2. Clinical symptoms, aetiology, disease-course and outcome

2.1. Disorders of arousal

Originally, the spectrum of arousal parasomnias involved three phenotypes 1) confusional arousals, 2) sleepwalking (somnambulism) and 3) night terror [1]. Recently, sleep related eating disorder and sexsomnia (consuming and preparing food; engaging in sex during sleep) have been included as well. Those experiencing confusional arousals wake up partially from NREM sleep with confusion and disorientation. Sleepwalking is a condition with motor awakening and ambulation without conscious mental experience or recall. Night terror as the most dramatic phenotype, is characterized by abrupt partial awakenings from deep NREM sleep with behavioural (screaming and agitation) and autonomic signs of intense alarm. The confused person seems horrified without any object or dream-memories. In the end of the episodes, they are exhausted, as if escaped from danger.

2.2. Sleep related hypermotor epilepsy (SHE)

SHE is another spectral condition; denominating frontal and extra-frontal epilepsies recently characterized by the Bologna consensus conference [3]. In its mildest form, subtle arousal behaviours represent the ictal activity that are hard to discriminate from normal

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sleep-movements; stereotypy might help. In the second degree variant, arousal-movements are joined by abrupt motor automatisms with basal ganglia features (choreo-athetotic, kicking, boxing, whole body-, or bottom shaking, squatting). Alike in the DOA spectrum, the most severe variant is characterized by high-swing clapping and slapping movements with emotional/autonomic signs and escape behaviours reflecting fear and horror. The chain of ictal events might be protracted by pauses and restarts.

The paper of Derry et al [5] highlighted the similarity of DOA and SHE as well as the spectral continuity of subtypes within both groups. This emblematic study has revealed pathological arousals as common essential building stones of these conditions.

2.3. Views on DOA and SHE

DOA has attracted attention due to its relatively high prevalence and the occurrence of violent forms in adults [9].

Research shed special light on the pathological arousal mechanism underlying the episodes. Sleep-wake dissociation [10,11] and the local/regional (rather than global) character of sleep has been evidenced [12]. The discovery of the alternating-hemisphere sleep of big aquatic animals and birds of passage has contributed to the understanding of sleep dissociation [13–15].

In DOA, partially awake and partially sleeping states co-occur. Specifically, during sleep terror episodes, such dissociation evolves between an activated salience network (normally activating when something subjectively salient happens) and a sleeping fronto-dorsal cognitive network [16–20].

The hubs of the salience network overlap with both the seizure-onset zones of successfully operated SHE patients [21] and the activated region of DOA (Figs. 1 and 2).

In a congruent approach, SHE has been set against absence epilepsy; SHE as the epilepsy of the arousal-system; versus absence epilepsy as the system-epilepsy of sleep promotion [22].

Loddo et al [23] investigated in a large patient population undergoing video-EEG monitoring for epilepsy-surgery, the scale of different-severity seizure-types of SHE. They classified them in three classes such as SAMs (sleep related arousal movements); RAMs (rising arousal movements); and CAMs (complex arousals with ambulatory movements); constituting the spectrum of epileptic arousals within the SHE framework.

Parrino et al [24] analysed the sleep-relations of frontal lobe epilepsy. Patients had increased wake-time after sleep-onset and decreased duration of slow wave sleep.

Ninety percent of NREM-seizures occurred during a cyclic alternating pattern (CAP) sequence, in association with a phase A1, mainly in the first sleep cycles. Seizure-frequency decreased together with the decline of deep sleep during the night. In other words, seizures coupled with CAP A1 (slow wave-type) micro-arousals i.e. anti-arousals promoting sleep. Since anti-arousals reflect a high homeostatic pressure and their frequency decreases in line with it; the distribution of seizures is determined by sleep homeostatic regulation; “seizures wear the fingertips of slow waves” [24].

3. The link of slow wave-bistability with arousing stimuli in NREM sleep

As a general rule of functioning, the sleeping cortex may respond to sensory stimulation in two opposing ways; providing an interface between the sleeping brain and the environment. The so called bistability of cortical sleep-slow waves embodies this enigmatic phenomenon. During high homeostatic pressure periods, an afferent stimulus activates a high-amplitude negative slow wave underlined by the synchronous hyperpolarization of cell membranes. It is not associated with $>$ 20 Hz rhythms and neutralizes the arousing effect of the stimulus immediately. The negative wave is followed by a lower amplitude EEG-positive slow wave with coalescent spindles and ripples promoting cognitive work-up [25]. This biphasic alternation is also seen in the well-known K-complex of N2 sleep and in the ~1 Hz slow oscillation’s up-and down-states of N3 sleep as well.

DOA-episodes typically appear when the first or second sleep cycle’s descending slope turns to ascending; following a movement-related anti-arousal and a slow wave (CAP A1). The sleep-distribution of SHE is similar, and its ictal arousals are often preceded by CAP A1 slow waves [24].

The presence of slow waves at the onset of sleep terror episodes had been described in the literature earlier. Canadian [26] and other articles [27,28] highlighted that EEG slow wave-synchronization (high voltage delta waves) during NREM sleep, had occurred more often in sleep terror patients than in controls; suggesting that “delta power and EEG synchrony may be important physiological markers of sleep terror presence and intensity”.

The bistable working mode manifests in fronto-medial CAP A1 slow waves [29,30].

Bistability can be evoked by the ascending brainstem arousal system [31] or in response to arousing stimuli.

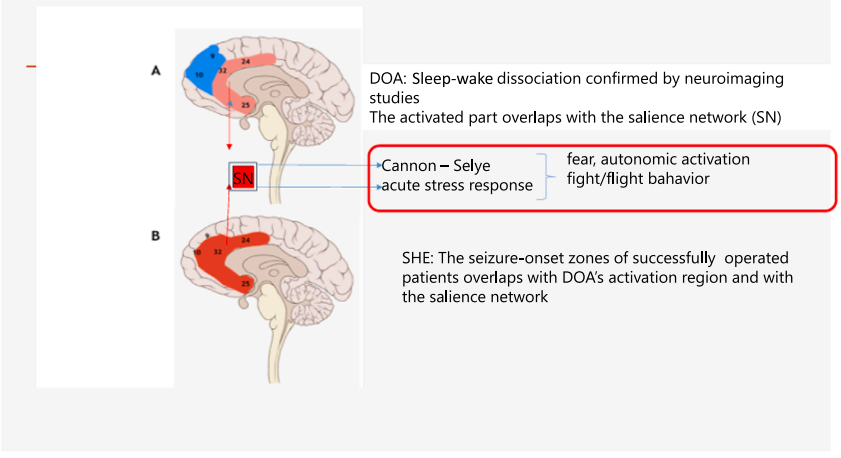

Fig. 1. Inter-links of the circuits of disorders of arousal (DOA) and sleep-related hypermotor epilepsy (SHE). (A) Sleep-wake dissociation in DOA episodes. The overlap of the activated states of DOA is confirmed by neuroimaging studies with the hubs of the salience network (see the 2nd figure). (B) The overlap of the activated fields of SHE, DOA and the seizure-onset zones of successfully operated SHE patients. Between the two schematic brain medial surface-drawings, we indicated the strong relation of activated fields (DOA and SHE) with the ignition of the Cannon-Selye acute stress response. This can be seen in the agitation (hypermotor and fearful) symptoms of both conditions.

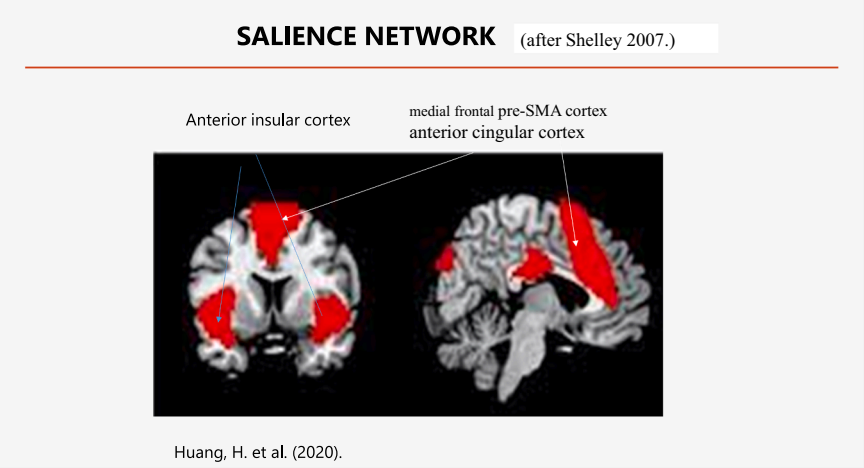

Fig. 2. Schematic picture of the salience network's hubs (red) shown in coronal and sagittal view (After Selley 2007) Halász P, Timofeev I, Szűcs A. Derailment of Sleep Homeostatic Plasticity Affects the Most Plastic Brain Systems and Carries the Risk of Epilepsy. *J. Integr. Neurosci.* **2023**, 22(5), 111. (with permission).

4. Mutual links of DOA, SHE and the acetyl-cholinergic arousal mechanism

SHE and DOA manifest similar syndrome-spectra displaying different intensity and complexity pathological arousals. NREM parasomnias start in childhood and may persist (or start) in adulthood; the adult variants manifesting more violence in the episodes [9].

In SHE, the abnormalities of the nicotinic acetyl-cholinergic system are confirmed [32] and genetically underpinned [33]; contrasting DOA, where such abnormalities have never been reported (notably, not much searched).

In other words, DOA's genetic background and link with SHE are supported by family and population-genetic studies [34], but the molecular genetic evidence is scarce.

The thalamus and frontal cortex are rich in cholinergic fibres, originating from the basal nucleus of Meynert, providing the most robust cholinergic input [37]. Since considerable body of evidence indicate that acetylcholine plays an important role in arousals from NREM sleep [35–37], an acetyl-cholinergic mechanism may be involved in both conditions.

The dynamic structure of sleep is shaped by the flexible balance of reciprocal antagonistic twin-systems; the wake-promoting ascending reticular system of the brainstem and the posterior hypothalamus, versus the anterior hypothalamic sleep-promoting system [38,39] The recognition of micro-arousals [40] in NREM sleep has supported the shaping role of arousal-activity. The studies on the arousal-related micro-structure of NREM sleep, have led to the recognition of the CAP [41], a micro-system under homeostatic control; protecting sleep against perturbations and highlighting the arousal-regulation of NREM sleep [42].

5. Controversies around the SHE concept

SHE is a rare (1.8/100 000 [43]), yet heterogeneous condition, constituted by two main subgroups.

One is determined by a structural lesion frequently related to focal developmental anomalies such as cortical dysplasias. Due to an inherent epileptogeneiticity of those lesions, there is abundant sleep-related spiking [44,45]. Seizures typically occur in sleep, and just two thirds of patients respond to pharmaco-therapy. In certain histology-types good surgical outcomes can be achieved, therefore the level and availability of healthcare has a determinant role for patient-outcome (also here).

In the second subgroup, no lesions can be detected by neuroimaging, and the epileptiform EEG symptoms are scarce both interictally and ictally [46,47]. Due to deceptive and misleading symptoms, diagnostic difficulties may arise.

Licchetta's study [48] supported the dichotomy of the SHE population. They studied the long-term outcome of SHE including 139 patients (86% sporadic and 14% familial). Sixteen percent of patients had brain abnormalities; 22.3% achieved seizure freedom within 5 years, and 77.65% continued to have seizures. An underlying brain lesion was more frequent among the latter, seizing group. The authors concluded to a poor prognosis of SHE suggesting that the outcome was primarily the function of aetiology.

Gibbs et al [49] found four characteristic semiology-patterns in SHE, depending on the seizure-onset zone.

Supporting the heterogeneity of nocturnal frontal lobe epilepsy (later termed SHE), Nobili et al [50] using intracranial electrodes, have shown multiple types, durations, intensities and complexities of epileptic discharges.

Recently we raised that some of the semiology-elements of hypermotor seizures are actually non-epileptic automatisms; rather, they might manifest the Cannon-Selye stress response activated by the salience network, which in turn, is ignited by the ictal activity of the anterior cingulate, insular and medial frontal regions [20].

6. SHE and epileptogenesis

According to the emerging system-epilepsy concept the epileptic networks evolve upon the most plastic brain systems by the upregulation of excitability there [51–55]. In this epileptic derailment, NREM sleep may have essential role.

The synaptic exhaustion due to daytime activities is expressed by the increase of slow oscillations (the measure and substrate of homeostatic power) [56–58]. Synapses are restored during NREM sleep by the down-scaling (decay) of this slow-activity across the night. The abundant epileptic activity in electrical status electricus in sleep (ESES) may obstruct this slow wave decay. Bölsterli [59–61] made a graphical EEG-method to demonstrate this lack of slow wave-decay during the night sleep of ESES patients, while after the expiry of the ESES pattern (spontaneously or in response to treatment), it has restored.

These data suggest that epilepsy is an inbuilt risk of human brain development; epilepsy is a price of plasticity [56–58]; or more precisely, of sleep homeostatic plasticity. This mechanism is exampled in post-traumatic and lesional epilepsies [62,63].

7. The name of the SHE spectrum

The name 'sleep-related hypermotor epilepsies' given by the Bologna

Conference [3] emphasizes sleep-relatedness of the involved conditions. However, the term 'sleep-relatedness' actually hides the actual arousal-relatedness from NREM sleep. Even the most severe hypermotor seizures manifest chaotic escape behaviours; in other words, "fearful arousals" [20]. This approach highlights these conditions as epilepsies of the arousal system; where the upgrading (exaggeration) of arousal-function leads to epilepsy.

8. Conclusion

This work does not offer any real solution for the dilemma: what is the relationship between DOA and SHE. We try to highlight the links, rather than the practical differences overwhelmingly discussed in the literature.

We aimed to point out the multiple uncertainties surrounding the parallel spectra of these conditions and discuss their interrelations beyond taxonomical difficulties. A shared feature of DOA and SHE is their very similar link with NREM sleep's micro-structural dynamics, shedding some light to the relationship of the sleeping brain with its inner and outer environment.

Declaration of competing interest

The authors declare no conflict of interest.

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