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Nocturnal motor events in epilepsy: Is there a defined physiological network?

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HIGHLIGHTS

- Nocturnal movements have consistent power changes in a physiological network.
- Nocturnal movements can be influenced by epilepsy, increasing the frequency and magnitude of events.
- Similarities in first clinical sign and movement semiology may suggest onset within the network.

ABSTRACT

Objective: Paroxysmal nocturnal movements in epilepsy are a recognised phenomenon, however, the mechanisms that produce them and the effect of the underlying epilepsy still remains elusive. In this study, 10 patients were studied to define the cerebral networks corresponding to these movements and explore how epileptiform activity modulated them.
Methods: We compared the change in power of the 25–250 Hz frequency band using event-related synchronization of all stereo-EEG electrodes implanted, during a baseline segment, during nocturnal movements and seizures.
Results: The underlying network activated during these paroxysmal movements comprised the insula, anterior cingulate, premotor areas and orbitofrontal regions. Three groups emerged, (1) complete overlap, (2) no overlap and (3) partial overlap of ERS changes of the epileptogenic zone within the proposed network and correlation of semiology between nocturnal movements and seizures.
Conclusion: We conclude that nocturnal movements are due to a complex interplay within this physiological network of defined anatomical regions. Epileptic activity had significant impact on nocturnal movements but was not required for generation.
Significance: Where the semiology of the first clinical sign of a seizure consistently matches a patient's nocturnal movements, we suggest that the underlying epileptogenic zone is potentially located within this defined network.

1. Introduction

Motor phenomena during sleep and wake transitions are a common finding. They reflect a dramatic interplay between brainstem and forebrain modulatory systems, resulting in an alteration in muscle tone and autonomic responses (Llinas and Steriade, 2006). Hypnic jerks (hypnagogic jerks, sleep starts), for example, are physiological, sleep related movements, resulting in brief, non-clonic contractions of the whole body or isolated segments (Vetrugno and Montagna, 2011). It has long been observed in epilepsy patients, particularly in nocturnal frontal lobe epilepsy (NFLE), that sleep related movements might be far more prominent in their physical manifestation as well as the frequency of occurrence at night (Lugaresi and Cirignotta, 1981; Oldani et al., 1996; Provini et al., 2000). These sleep movements, seen in non REM sleep, have been classified into two main types, based upon their duration and semiology. They include: paroxysmal arousals- comprising stereotyped head or trunk elevation, lasting 5–10 s and minor motor events (MMEs)- brief (<5 s) limb, trunk or face

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movements (Tinuper et al., 1990; Provini et al., 1999; Provini, Plazzi, Montagna and Lugaresi, 2000; Gibbs et al., 2016).

Initially, MMES were considered to be attributable to epileptic phenomena for a variety of reasons. These included intracranial correlation with an epileptic fast discharge at onset (Nobili et al., 2005) and similarities in semiology corresponding to the more pronounced/typical seizures (Sforza et al., 1993) and a high frequency of stereotyped fast movements during sleep (Terzaghi et al., 2007). It was hypothesized that MMEs involved the minimal amount of epileptogenic tissue within a larger framework of the epilepsy (Sforza et al., 1993). However, due to the lack of EEG findings in both scalp recordings and in the majority of intracranial recordings (Terzaghi et al., 2007), MMEs were not considered to be true epileptic phenomena. Rather, their motor manifestation was deemed to be the consequence of the epileptiform discharge causing a brief arousal from sleep, resulting in movement (Nobili et al., 2005; Parrino et al., 2006; Terzaghi et al., 2007; Gibbs et al., 2016).

Stereo electroencephalography (SEEG) recordings during MMEs have identified certain cerebral regions of involvement. These include the supplementary sensorimotor area (SMA), the frontal and cingulate gyrus and the anterior and middle frontal gyri (Nobili et al., 2005; Terzaghi et al., 2008; Gibbs et al., 2016). Epileptiform activity was reported as fast spiking and superimposed low amplitude fast discharges. Only 2/3 of the epileptiform discharges though were found to have been associated with MMEs (Terzaghi et al., 2007). The major seizures were reported to involve the same anatomical regions as MMEs, along with the same underlying epileptiform discharges, but in a sustained and evolving discharge (Nobili et al., 2005).

In addition to MMEs and paroxysmal arousals, there also exist physiological non-periodic myoclonic movements known as hypnic/hypnagogic jerks (American Academy of Sleep, 2005). These are seen in sleep onset, and may also be associated with K-complexes (Parrino et al., 2006), making them indistinguishable from MMEs and PAs on scalp EEG.

We present ten patients with nocturnal movements who underwent stereo-EEG for their refractory epilepsy. Signal processing was performed in order to provide more insight into the underlying generation of these movements.

2. Methods

2.1. Subjects

Patients admitted to the Mater's Advanced Epilepsy Unit for invasive monitoring using Stereo-electroencephalography (SEEG), as part of the surgical evaluation for their refractory epilepsy between May 2017 and February 2018 were included in the study. Implantation of the SEEG electrodes was according to the Talairach stereotactic method and based on the pre-surgical evaluation. Implantation maps are provided in the Supplementary Items.

Between ten and eighteen multicontact MicroDeep (DIXI medical, Besançon, France) semi-flexible platinum electrodes were implanted. Each electrode diameter is 0.8 mm with a contact length of 2 mm and an intercontact insulation length of 1.5 mm. The exact positions of the electrodes were verified by visual analysis of a co-registered in situ CT with a MRI. SEEG recordings were made on a Nihon Kohden, EEG-1200 system, with a 1 kHz-sampling rate.

All patients provided informed consent and the study was approved by the local ethics committee.

2.2. Movement markers

Prior to marking, appropriate files were first selected. These files were extracted from a patients record when (1) the time of recording was between 11pm and 3am, which was dependent on when files were segmented for storage and (2) the patient was asleep for the entire 90-minute file.

These selected files were then manually annotated with what limb, and time the movements occurred, with no exclusion criteria, to be used in the signal processing stage. These markers provide the onset of movement, which were identified by analysis of high-resolution, with infrared, video and EMG of both Bicep brachii muscles. Each patient's seizures were also marked with no exclusion criteria, except if the patient was already moving during the onset of the seizure.

2.3. Signal processing

Processing of each channel within the study had four steps; (i) Preprocessing, (ii) filtration, (iii) conversion into event-related synchronization (ERS), and (iv) extraction of an ERS segment for each nocturnal movement. All Processing was performed offline using custom MATLAB (MATLAB 8.5, The MathWorks Inc., Natick, MA, 2015) programs.

2.3.1. Preprocessing

Contacts external to the cortical surface were excluded with all remaining SEEG contacts digitally re-referenced into a bipolar montage of adjacent contacts, creating the channels discussed in this article. Each channel was filtered to remove power line interference using a forward-then-reverse finite impulse response (FIR) filter (Hamming, 1000 Pole) with 2 Hz bandwidth centered on 50 Hz.

2.3.2. Filtration

Each channel was filtered using a bandpass, 25–250 Hz, forward-then-reverse FIR filter (Hamming, 1000 Pole) to eliminate time shifts introduced by filtering (Fig. 1b, black). Each channel was filtered in a single pass with a section removed at both ends to avoid edge effects. A series of filters were trialed, with the selected filter producing the greatest changes during the events captured, and also providing antialiasing of higher frequencies. A Hilbert transform was applied to each channel, with the absolute of it kept as the amplitude of the frequency band of interest (Fig. 1b, red).

2.3.3. Conversion to event-related synchronization

ERS is a measure of amplitude change compared to a baseline value, which is expressed in an approximately linear scale. ERS was used as it expresses both positive and negative power changes with equal magnitude rather than amplitude's logarithmic scale. To calculate the baseline, thirty randomly spaced segments of ten seconds, at least ten seconds from any annotation (movement or artefact) were extracted from the amplitude time series. These segments were concatenated then averaged to produce a single value representing the baseline (Fig. 1c). This was repeated for each channel's amplitude time series.

Subtracting the baseline value from the corresponding amplitude series, then dividing the result by the same baseline, converts it into ERS, as given by Eq. (1). ERS values are then multiplied by 100 to express them as a percentage.

2.3.4. Extraction of ERS segments

A section ±10 s around each movement marker, for all channels was extracted from the ERS times series created (Fig. 1d). This forms a matrix with dimension [Number of Markers, Number of Channels, 20 s]. Averaging across the movement markers generates the ERS of nocturnal movements.

A section ±10 s around the movement onset for all seizures is also extracted and are averaged to create the ERS of a seizure.

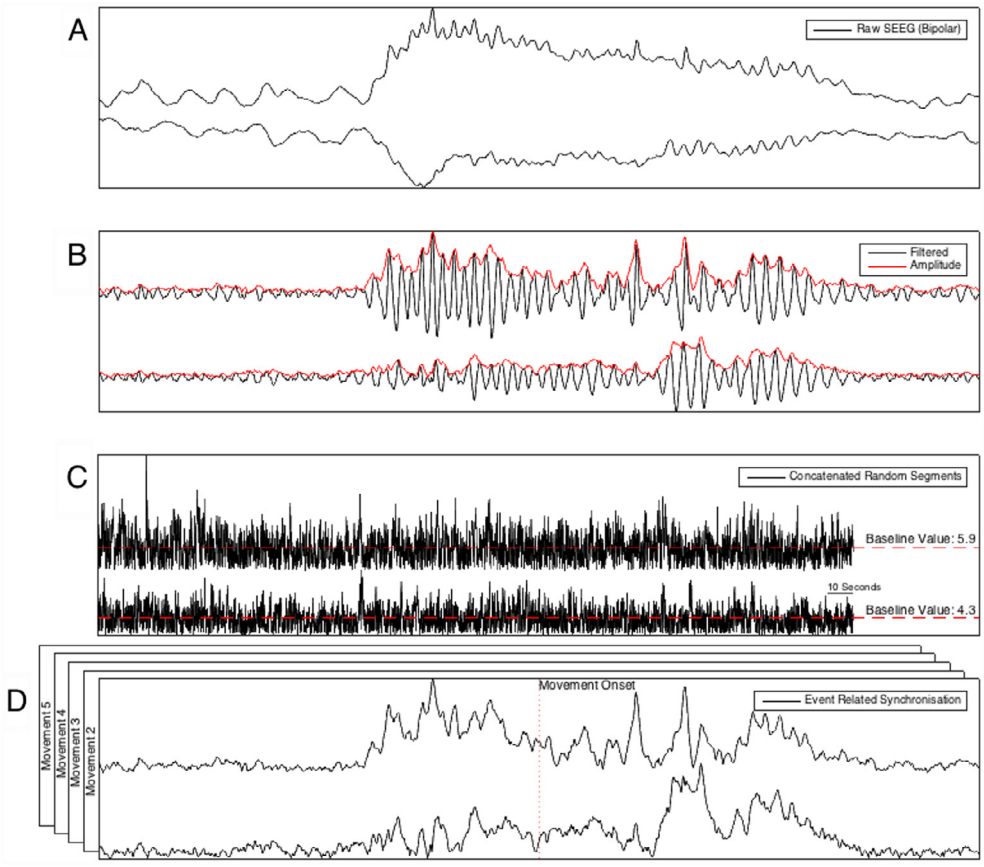

Fig. 1. Process of converting to event related synchronization. (A) Two Channels of Raw SEEG, (B) Filtered SEEG at 25–250 Hz in black, amplitude of the filtered channels in red, (C) Randomly selected segments concatenated from each channel, then averaged to calculate the Baseline value, (D) Extraction of segments surrounding movement markers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$$Percentage\ \ Change = \frac{Amplitude - Baseline}{Baseline} \times 100 \qquad (1)$$

where

$$Percentage\ \ Change = \left\{ \begin{array}{c} ERS, \quad Percentage\ \ Change > 0 \\ ERD, \quad Percentage\ \ Change < 0 \\ Baseline, \quad Percentage\ \ Change = 0 \end{array} \right\}$$

2.3.5. Anatomical grouping

Each of the contacts, on every electrode, was reviewed for location using co-registered CT to MRI and EEG signal analysis. In total, thirty anatomical regions were sampled. The number of contacts pertaining to each region is provided in Fig. 2.

2.3.6. Statistical testing

The ERS segments for each channel were normalized per patient to account for differences in the ERS ranges. Twenty percent of channels, from each patient were then collected which had the greatest mean ERS value, either positive or negative, during the nocturnal movements. Comparisons were then performed using a *t*-test on the normalized ERS of this top response group with an alpha value of 0.05 considered statistically significant.

2.3.7. Seizure and nocturnal movement ERS correlations

Three groups were established, based on the correlation in ERS during seizures and nocturnal movements. The groups, strong, weak and no correlation, identify the level of similarity of all recorded channels during both events. This was identified by visual analysis of the ERS, where a strong correlation was regarded as near identical change in ERS surrounding the onset of movement in both seizure and nocturnal movements. A weak correlation was decided when some channels were clearly well correlated, but also some additional channels in either the seizure, or nocturnal movements, were fluctuating independently. No correlation was decided when there was no pattern in ERS that both seizures and nocturnal movements shared surrounding the onset of movement.

3. Results

In total 10 patients (mean age: 32 ± 13 years; range 16–53 years) were included in the analysis, their epilepsy details are outlined in Table 1 along with the number of movements and period of recording. We recorded data from 1594 SEEG contacts (mean 159.4; STD 30; range 120–211) which were implanted along 151 electrodes (mean: 15.1; STD 2.02; range 11–18) with an additional 140 (mean 14; STD 4.83; range 5–22) contacts excluded from analysis as they were external to the cortical surface. An implantation map of the electrodes for each patient is provided in the Supplementary Items. All patients had frequent episodes during sleep, comprising abrupt limb, hand, head or face movements with no limb exclusion. The movements were phasic and usually lasted 1–2 s. Scalp recordings during this time, confirmed stage 2 sleep. While often associated with the end of a K-complex, movements were also associated with sleep spindles. No patient was identified as having NFLE. Common movements from our population included: finger or wrist extension or flexion, elevation of the head from the pillow, foot extension, flexion, inversion or eversion, unilateral face pull, mouth deviation and opening. Each patient had a stereotypical movement that would account for approximately

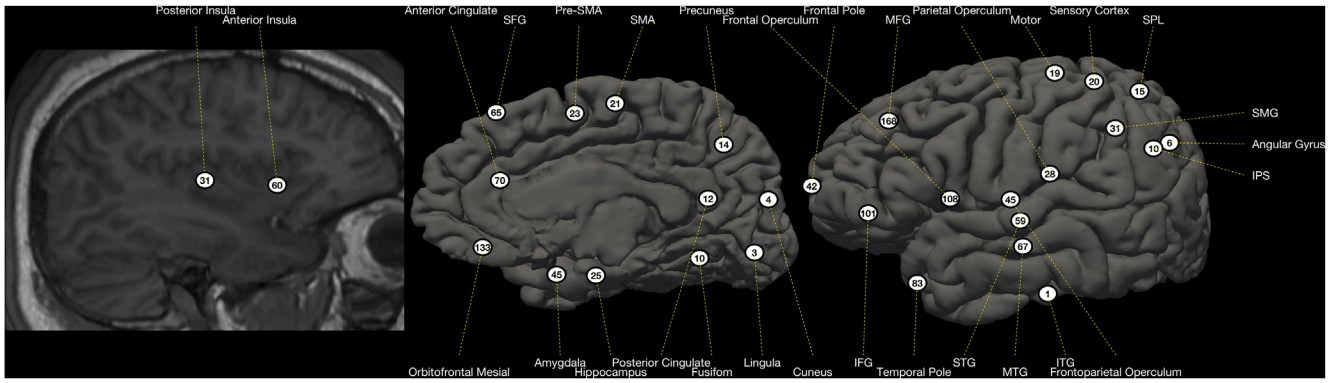

Fig. 2. Number of contacts analyzed in the study, grouped and shown anatomically.

Table 1
Patient and nocturnal movements recording details.

Patient	Age/sex	Epilepsy duration (Years)	Sleep analysed (min)	Movements recorded	Before seizure rate (per 90 minutes)	After seizure rate (per 90 minutes)	Location of epileptogenic zone on SEEG	Surgery
A	18/M	13	180	27	9	18	Left pars orbitalis	Left pars orbitalis
B	35/F	6	90	20	20	–	Widespread onset; right insula and dorsomesial prefrontal network (Pre-SMA, anterior cingulate and orbitofrontal)	Non-surgical
C	16/F	8	270	76	16	38	Right mesial temporal	Right ATL
D	27/M	17	270	89	14	61	Left anterior long gyrus of the insula	Awaiting surgery
E	22/F	7	180	18	–	10	Focal left mesial temporal	Left ATL
F	53/F	31	180	67	29	38	Bilateral parietal operculum	Non-surgical
G	51/M	43	180	126	38	88	Right insula and anterior cingulate	Awaiting surgery
H	30/M	26	270	142	57	28	Left superior frontal gyrus	Awaiting surgery
I	46/M	16	90	24	–	24	Right mesial temporal	Right ATL
J	26/M	19	180	44	–	22	Widespread onset; left insula, Pre-SMA, anterior cingulate, bilateral orbitofrontal	Non-surgical
Total			1890	633				

60% of their nightly movements, with several less frequent movements accounting for the remaining.

We identified an increase of 147% in nocturnal movement frequency following a seizure in 5 out of 6 patients. These patients had both, a seizure free sleep period post implantation, then a prolonged sleep period after seizures, which were analyzed. The 6th patient (H), from this group, though decreased their nocturnal movement frequency by 51%, explained by the administration of midazolam due to a prolonged seizure.

We also observed that the nocturnal movements became more exaggerated, and correlated with the increase in number of events following a seizure. For example, pre-seizure some patients only had a single finger extension, which later involved multiple fingers in both hands post seizure. In another patient, subtle foot flexion became more sustained foot tapping post seizure. While there was a change in power at these times, it was not significant.

3.1. Defining the physiological network

During analysis we visually identified four regions that that had consistent ERS changes during nocturnal movements, which we have considered to be part of a physiological network. These regions are the insulo-opercular, anterior cingulate, orbitofrontal region and together the dorsolateral prefrontal cortex (DLPFC comprising the middle frontal gyrus and superior frontal gyrus) primary motor and mesial premotor areas (SMA, PreSMA). The latter region is considerably larger, as implantation targets varied in that region on a case-by-case basis.

We then examined the channels from the top normalized ERS groups to identify the concentration of channels that were experiencing high ERS changes and were from our network. We found that channels recorded in our four regions made up a 78% of channels in the top normalized ERS responses during nocturnal movements. We then compared the top normalized ERS responses from our four regions, against the other channels remaining within the top 20% of ERS change. We found that each of our regions, the insulo-opercular, anterior cingulate, orbitofrontal region and together the DLPFC, motor and pre-motor regions were all statistically significant compared to the combined anatomies remaining in the top group as seen in Fig. 3.

3.2. Seizure impact on the physiological network and resulting semiology

Further analysis found that in 7 patients (A, B, D, F, G, I and J) the semiology of the motor manifestation of the nocturnal movement

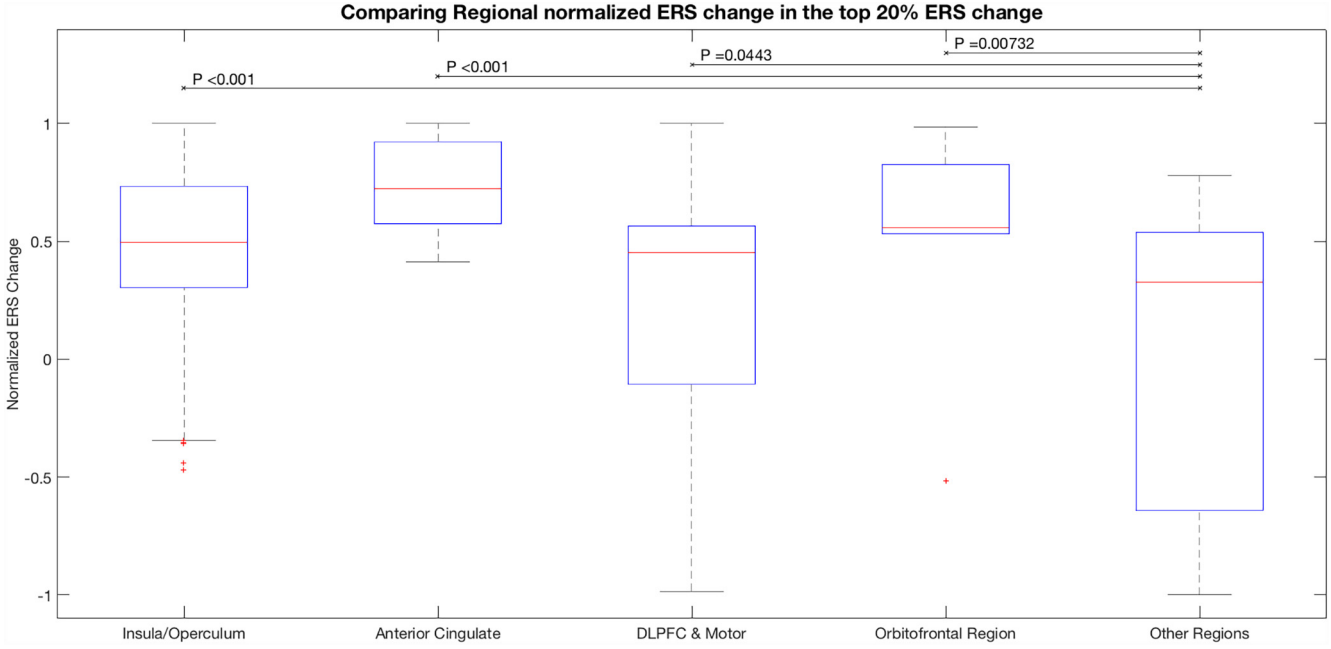

Fig. 3. Normalized ERS changes during nocturnal movements and *p* values for comparing each region to the 'Other regions' using a two sample *t* test.

was also seen at the start of the clinical onset of seizures, shown in Table 2. And in some cases, if a seizure occurred while awake, the same movement would occur as was seen during sleep.

As our cohort of patients all had epilepsy, and we had found that seizures had an immediate effect on the frequency, amplitude and semiology of their nocturnal movements, we then considered if the nocturnal movements were due to epileptiform activity, or rather a disruption of a physiological processes caused by epileptic activity.

The strongly correlated group had two patients (D and J) whose ERS changes during nocturnal movements was a clear subset, albeit with lower amplitude, of their seizures ERS changes as seen in Fig. 4. This group had highly stereotypical nocturnal movements that exactly matched the semiology at the seizure onset. This group also had the most significant ERS changes during nocturnal movements, upwards of 100% increase. In this group, the location of the EZ, clinically defined by SEEG and identified by ERS changes, was confined to the defined network.

The second group, no correlation, had a complete separation in the ERS activity of nocturnal movements and seizures. This group also had the lowest ERS response during nocturnal movements, only noticeable when compared to baseline and seizure events as seen in Fig. 5. This group's movements were the smallest in magnitude compared to the other groups and the semiology of the nocturnal movements was less stereotyped. Furthermore, there was no correlation of the semiology of the nocturnal movements with seizure onset. In this group, the localization of the epilepsy did not have a primary effect on these regions, rather they were involved through secondary propagation.

The third group, weak correlation, was made up of 7 patients (A, B, E, F, G, H and I), had ERS changes during nocturnal movements that did not completely correspond to their seizures. Specifically, a network of channels would experience ERS changes during a seizure but not all those channels involved would be active during nocturnal movements, or vice vera. This group had more varied results when comparing the semiology of nocturnal movements and seizures, with some preceding seizures with typical nocturnal movements with other not performing them at all. The changes in ERS again were more variable then the other groups, ranging from around 15–60 percent, but were consistent individually over multiple nights and nocturnal movements.

As expected from a variety of epilepsies' no common pattern of ERS changes emerged in terms of anatomical involvement or magnitude of the ERS changes during a seizure. Even where the ictal onset arose from a common area, such as the insula in patients D, G and F, the type of movements, the magnitude of ERS changes and the affect of seizures on the frequency and amplitude of the movements varied considerably.

Table 2
Occurrence rates for nocturnal movements and in seizure semiology.

Patient	Nocturnal movement semiology occurrence	Seizure first clinical sign
A	Fingers 60%, Arms 20%	Finger tapping
B	Arms 60%, Fingers 30%	Fingers tapping
C	Feet 42%, Legs 32%	NS
D	Jaw 55%, Legs 26%	Jaw movement
E	Feet 28%, Legs 28%	NS
F	Fingers 73%, Feet 16%	Finger movement
G	Feet 44%, Fingers 24%	Finger movement
H	Fingers 41%, Head 25%	NS
I	Hand 71%, Shoulders 13%	Arm and shoulder jerk
J	Arms 55%, Fingers 21 %	Finger movement

NS – First clinical sign was not similar to nocturnal movements.

4. Discussion

Pathological nocturnal movements such as nocturnal paroxysmal dyskinesias, paroxysmal arousals, sleep wandering and minor motor events have been associated with NFLE. However, due to the lack of associated epileptiform activity during such events, whether they represent seizures, has been disputed. Several groups using scalp EEG have concluded that nocturnal attacks have a deep frontal epileptic onset, but also mention the recording difficulties for this region (Lugaresi et al., 1986; Sforza et al., 1993; Oldani et al., 1996; Provini et al., 1999). More recently, intracranial recordings have found associations of these movements with seizures arising from the temporal (Nobili et al., 2004; Mai et al., 2005) or insula regions (Kaido et al., 2006; Ryvlin et al., 2006; Dobesberger et al., 2008; Proserpio et al., 2011).

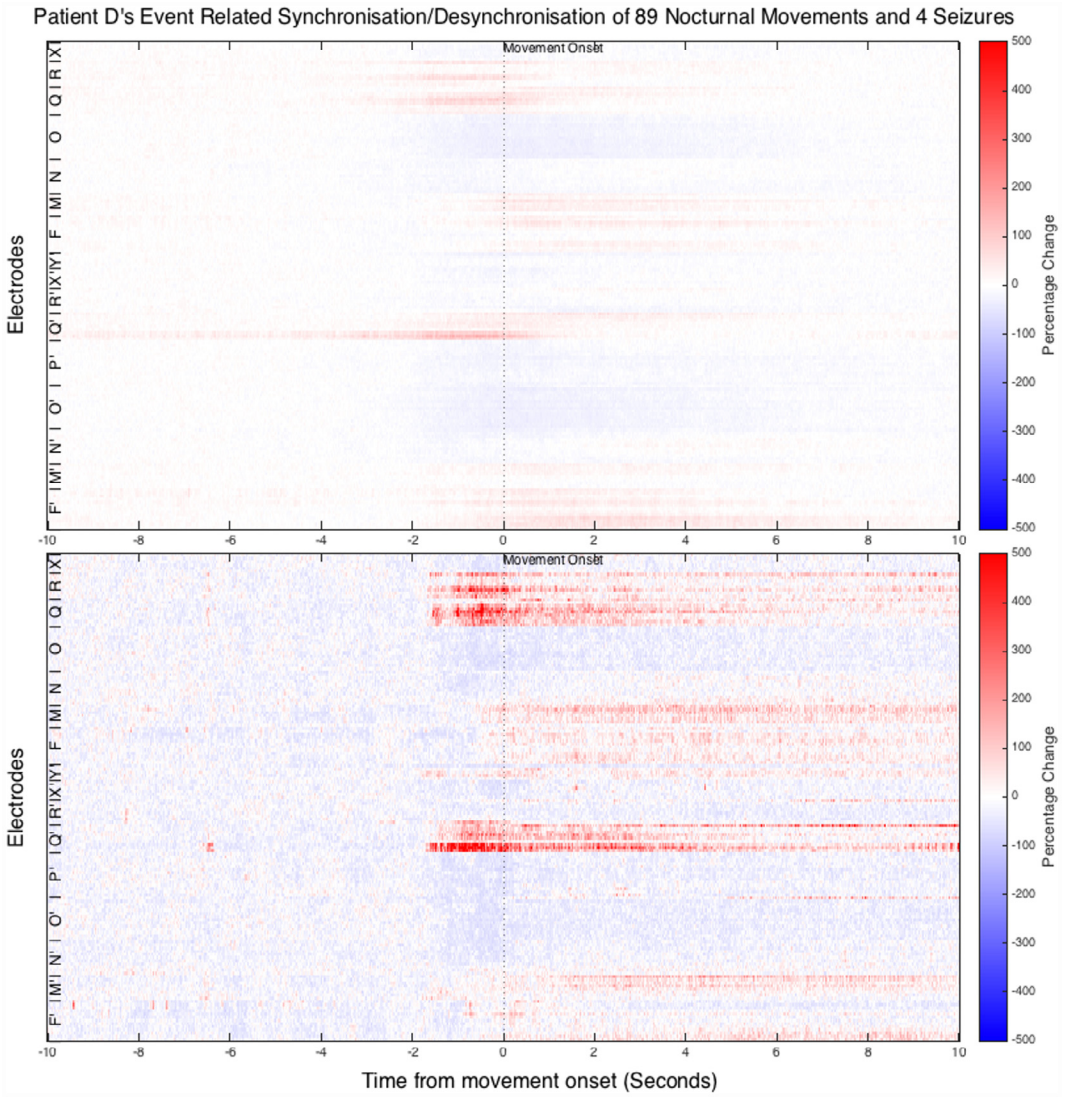

Fig. 4. Average change of patient D's 89 Nocturnal movements (Top) and 4 typical seizures (Bottom), a positive change, ERS, is coloured red, a negative change, ERD, is coloured Blue. Left sided electrode targets, F': SMA, M': Mid-cingulate, N': Pre-SMA, O': Orbitofrontal Region, P': Precuneus, Q': Posterior Insula, R': Anterior Insula, X': Posterior Cingulate, Y': Anterior Cingulate. (D) Right sided electrode targets, F: SMA, M: Mid-cingulate, N: Pre-SMA, O: Orbitofrontal Region, Q: Posterior Insula, R: Anterior Insula, X: Posterior Cingulate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The quasi-periodic occurrence of nocturnal movements has been attributed to a lack of inhibition to motor areas during transition between sleep states and arousal patterns (termed cyclic alternating patterns) and K-complexes (Sforza et al., 1993; Fusco et al., 1999; Provini et al., 2000; Zucconi and Ferini-Strambi, 2000; Nobili et al., 2006). These cyclic alternating patterns (CAP) may be periodically enhanced in NFLE resulting in an increase prevalence than in controls (Terzano et al., 1997). Interestingly, anti epileptic drugs, have been shown to reduce the frequency of nocturnal movement due to a lowered CAP rate (Terzano et al., 1997; Nobili et al., 2014) lending further arguments in support of a potential epileptic cause.

Alternate theories have proposed a disinhibition or, release mechanism, in the frontal cortex that can cause complex inborn motor behaviors such as biting, grasping and rhythmic leg movements (Tassinari et al., 2003; Tassinari et al., 2005; Gardella et al., 2006). Furthermore, disinhibition of prefrontal regions in frontal hyperkinetic epilepsies have resulted in both behavioural changes and increased manual motor activity, an observation seen in our study, where manual movements were the most common (Tassinari et al., 2005; Gardella et al., 2006).

We believe that the nocturnal movements we captured, minimal and minor by quantification according to Sforza et al. (1993) and Oldani, Zucconi et al. (1996) fall under a spectrum of nocturnal activities of a physiological nature, involving a defined cortical network, that is susceptible to epileptic influence.

Support for this comes from the consistent ERS changes through our cohort and other arousal literature (Peter-Derex et al., 2015). While the epileptogenic zone (Talairach et al., 1973) was variable in anatomical location amongst individual patients, activation of specific cortical areas were a requisite for movement. Four regions were identified with similar changes across all patients: The DLPFC and primary motor cortex, the insula, anterior cingulate and orbitofrontal regions. These regions contributed the largest ERS changes during nocturnal movements and were all statistically significant when compared to other channels experiencing ERS changes.

However, when the epileptogenic zone directly arose from one of these regions, the subsequent movements were more exaggerated in semiology and also matched the semiology of the prolonged seizure. Other groups share a similar opinion from different techniques, Picard et al. (2006) analysed several families

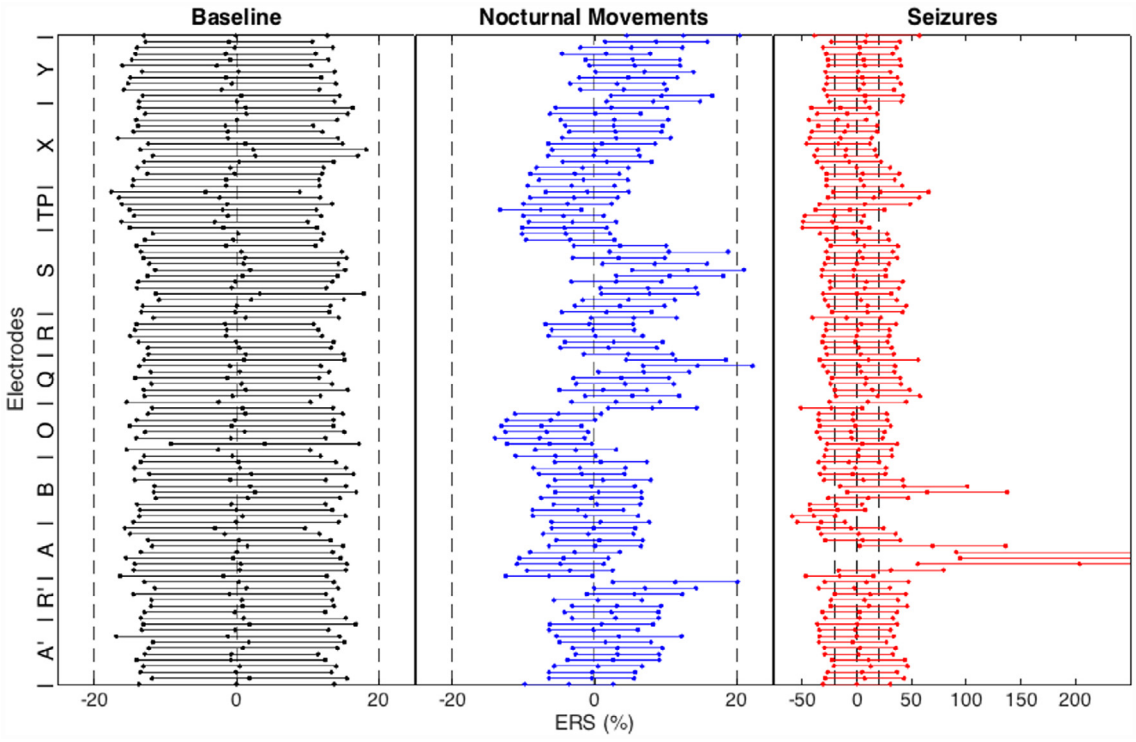

Fig. 5. Forest Plot of Patient C's Mean ERS ± SD of all implanted channels during baseline (Left), Nocturnal Movements (Middle) and Seizures (Right). Left sided electrode targets, A': Amygdala, R': Mid insula. Right sided electrodes, A: Amygdala, B: Hippocampus, O: Orbitofrontal, Q: Anterior insula, R: Mid insula, S: Anterior cingulate (left and right targets), TP: Temporal pole, X: Precuneus, Y: Middle frontal gyrus.

using imaging software and Terzaghi and Manni (2012) through case study identified the same network adding several anterior temporal structures (amygdala and hippocampus). In consideration of more pronounced nocturnal activity (eg sleepwalking), there is reported activation of the anterior cingulate region with persisting inhibition of other thalamocortical arousal systems (Bassetti et al., 2000).

The insula-cingulate network may be a key player in these movements. Connectivity between these regions is well established (Allman et al., 2011; Butti et al., 2013; Ghaziri et al., 2017). The Cingulate Motor Area (CMA), located in the lining of the dorsal anterior cingulate sulcus, is a major motor system, receiving input from the thalamus (Paus, 2001; Hatanaka et al., 2003) and directly projecting to both the primary motor cortex and spinal cord (Paus, 2001). Both these areas were key components activated in the nocturnal movements in our cohort of patients.

Modification in the orbitofrontal region may be a necessary mechanism to terminate the nocturnal movements. The inferior frontal cortex has been associated with inhibitory control tasks (Cai et al., 2014) in particular when accompanied by activation of the anterior insula during saliency processing (Menon and Uddin, 2010). In our cohort, suppression during nocturnal movements was seen in a similar ratio as the seizures.

5. Limitations

Inherit to SEEG, there exists a maximum sampling distance estimated to be approximately 1 cm around the electrical contacts (Caune et al., 2014). This limits the extent to which our research can record and we acknowledge that our electro-anatomical correlations (ERS of nocturnal movement) are subject to this constraint, of which is the basis of our results. In saying this, we re-reference our data, at the beginning of processing, into a bipolar montage, where it is expected that the channels derived are representative of the local activity between adjacent contacts. In addition to sampling distance, the volumetric space of brain that is recorded by SEEG is relatively limited, and is selected to identify the hypothesized epileptogenic zone and the common pathways to and from it. This potentially biases the visibility of neurological activity in regions less commonly implanted or could gives higher weight to those commonly recorded as equal coverage is not possible.

6. Conclusion

We have identified consistent power changes in the anterior cingulate, insula, DLPFC and motor cortices and the orbitofrontal region that we believe may be responsible for nocturnal movements. This network, and physiological process though can be impacted by epilepsy, which can increase the frequency of activity and the amplitude of movements.

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.05.033.

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