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Brain functional connectivity in sleep-related hypermotor epilepsy

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ABSTRACT

Objectives: To evaluate functional connectivity (FC) in patients with sleep-related hypermotor epilepsy (SHE) compared to healthy controls.

Methods: Resting state fMRI was performed in 13 patients with a clinical diagnosis of SHE (age = 38.3 ± 11.8 years, 6 M) and 13 matched healthy controls (age = 38.5 ± 10.8 years, 6 M).

Data were first analysed using probabilistic independent component analysis (ICA), then a graph theoretical approach was applied to assess topological and organizational properties at the whole brain level. We evaluated node degree (ND), betweenness centrality (BC), clustering coefficient (CC), local efficiency (LE) and global efficiency (GE). The differences between the two groups were evaluated non-parametrically.

Results: At the group level, we distinguished 16 RSNs (Resting State Networks). Patients showed a significantly higher FC in sensorimotor and thalamic regions ($p < 0.05$ corrected). Compared to controls, SHE patients showed no significant differences in network global efficiency, while ND and BC were higher in regions of the limbic system and lower in the occipital cortex, while CC and LE were higher in regions of basal ganglia and lower in limbic areas ($p < 0.05$ uncorrected).

Discussion and conclusions: The higher FC of the sensorimotor cortex and thalamus might be in agreement with the hypothesis of a peculiar excitability of the motor cortex during thalamic K-complexes. This sensorimotor-thalamic hyperconnection might be regarded as a consequence of an alteration of the arousal regulatory system in SHE. An altered topology has been found in structures like basal ganglia and limbic system, hypothesized to be involved in the pathophysiology of the disease as suggested by the dystonic-dyskinetic features and primitive behaviours observed during the seizures.

1. Introduction

Sleep-related hypermotor epilepsy (SHE), previously known as nocturnal frontal lobe epilepsy (NFLE), is a rare and peculiar form of focal epilepsy characterise by brief (< 2 min) seizures with stereotyped motor patterns, commonly "hypermotor" events, occurring predominantly during sleep (Provini et al., 1999; Provini et al., 2000; Tinuper and Lugaresi, 2002). The diagnostic criteria of SHE were recently revised during an international consensus conference (Tinuper et al., 2016). The differential diagnosis with other non-epileptic nocturnal paroxysmal events, namely parasomnias, can be a challenge (Bisulli et al., 2011; Licchetta et al., 2017; Nobili, 2007; Tinuper et al., 2011) since in SHE interictal and ictal scalp EEGs, as well as neuroradiological findings, are often unrevealing.

Hypermotor seizures were described to arise from various areas of the frontal lobe, as expected, but also from extra-frontal regions, such as more frequently in the temporal lobe, or in the insular cortex, but also in the parietal, occipital and opercular areas (Gibbs et al., 2016). Hyperkinetic automatisms and complex behaviours appear when the ictal discharge involves structures such as the cingulate, frontal and parietal regions, irrespective of its origin (Rheims et al., 2008). These observations suggest the hypothesis that the syndrome affects a broad

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Table 1
Demographic and clinical data of the patients' sample.

ID	Sex	AAE (yrs)	DD (yrs)	Seizures frequency 6 months before MR scan	AE therapy at MR scan	Diagnosis of SHE	Brain structural MRI findings
1	F	18	6	Seizure-free	CBZ	Confirmed	Negative
2	M	20	1	Multiple/night	None	Confirmed	Negative
3	F	28	3	Multiple/night	None	Clinical	Negative
4	F	29	24	1–2/night	CBZ	Confirmed	Negative
5	M	35	25	Multiple/week	OXC, PHT, LCS	Confirmed	L frontal heterotopia
6	F	36	29	Monthly	CBZ	Confirmed	Negative
7	F	42	34	Multiple/month-yearly	CBZ, TPM, CLB	Confirmed	Negative
8	M	44	30	Monthly	LTG, TPM	Confirmed	Negative
9	F	45	39	Monthly	CBZ, PB	Confirmed	Negative
10	M	46	32	Monthly	None	Clinical	Negative
11	F	49	23	Weekly	CBZ	Confirmed	L frontal FCD
12	M	50	38	Seizure-free	OXC	Clinical	Negative
13	M	55	48	Multiple/night	CBZ	Confirmed	L opercular-insular FCD

AAE: age at evaluation; DD: disease duration; AE: anti-epileptic; OXC = oxcarbazepine; PHT = phenytoin; LCS = lacosamide; CBZ = carbamazepine; TPM = topiramate; CLB = clobazam; PB = phenobarbital; LTG = lamotrigine; FCD focal cortical dysplasia.

scale of cerebral domains, hinting at a network rather than a localized disturbance process (Biraben et al., 2001).

To provide valuable insights in the pathophysiology of this syndrome, we used functional MRI (fMRI) technique to investigate brain functional connectivity (FC) during resting state, i.e. in the absence of any stimulation (Biswal et al., 1995; Lowe et al., 1998). Resting state fMRI is attractive for the simplicity of the acquisitions, but, as a counterpart, the interpretation of the results can be complicated by the amount of the analytic options and different pre-processing/processing techniques that yield subtly different types of information.

ICA (Independent Component Analysis) is a data driven approach that for fMRI data gives a set of statistically independent spatial maps, grouping together temporally coherent brain regions (resting state networks, RSNs) (Beckmann et al., 2005; McKeown and Sejnowski, 1998).

A recent analytical approach for brain FC is graph theory, which models the brain as a complex network represented by a collection of nodes and edges (Bassett and Bullmore, 2009) and provides a promising tool for describing and characterizing the topological features and the organization of brain networks (Wang et al., 2010).

Both methods have already been applied to fMRI data in the most common forms of epilepsy. ICA-fMRI studies mainly found decreased functional connectivity in temporal lobe epileptic patients compared to controls (Voets et al., 2009; Zhang et al., 2009). Graph analyses have identified a less efficient brain network organization in temporal lobe epilepsy albeit with either a more regular (Wang et al., 2014) or a more random network topology in both temporal lobe and idiopathic generalized epilepsy (Liao et al., 2010; Zhang et al., 2011).

The purpose of this study was to evaluate FC in SHE patients compared to healthy controls. We firstly used the explorative and data-driven approach of ICA to determine whether resting state fMRI can detect RSNs abnormalities in SHE patients, then, in order to further explore the organization of these complex systems, we applied graph theory. To the best of our knowledge, this is the first study that attempts to highlight possible alterations in brain FC of SHE patients.

2. Materials and methods

2.1. Subjects

Thirteen SHE patients (age = 38.3 ± 11.8 years, range 18–55 years, 6 males, disease duration = 25.6 ± 14.6 years, age at onset = 12.6 ± 6.9 years) and thirteen age and sex matched healthy controls (age = 38.5 ± 10.8 years, range 19–54 years, 6 males) participated to the study.

Diagnosis of SHE was made according to the criteria recently proposed by Tinuper et al. (2016). Ten out of thirteen patients had a diagnosis of SHE confirmed by video-EEG, while three had a clinical, video-documented diagnosis. Six patients had infrequent attacks (monthly or yearly attacks), while seven patients had weekly or nightly attacks. All but two were being treated with antiepileptic drugs. Further clinical details can be found in Table 1 and in supplementary Table 2.

All the subjects gave written consent to study participation, and the study was approved by the local Ethical Committee.

2.2. Brain MRI acquisition

Acquisitions were performed with a 1.5 T GE Signa HDx 15 scanner equipped with an 8-channel head coil. All the subjects underwent a standardized MR protocol that included 9 min of resting state fMRI acquired in two consecutive runs. Subjects were instructed to lie still with their eyes closed without falling asleep, trying not to think about anything specific. The acquisition sequence was a gradient-echo echo-planar imaging (GE-EPI, TR/TE = 3000 ms/40 ms, 34 pure axial slices *per vol.*, 90 vol. *per run,* spatial resolution = 1.875 mm × 1.875 mm × 4 mm). For each run, five initial volumes were not saved to account for the MR signal equilibration.

The MR protocol also included a 3D high-resolution volumetric T1-weighted brain structural image (FSPGR, fast spoiled gradient-echo, pure axial slices, TR/TE = 12.3 ms/5.2 ms, FOV = 25.6 cm, nv = 256, 1 mm isotropic).

2.3. Data pre-processing

The data pre-processing was conducted using FSL (Jenkinson et al., 2012, Smith et al., 2004). For each subject, the two resting state runs were pre-processed separately. Functional images were corrected for slice timing and head-motion (MCFLIRT, Motion Correction FMRIB's Linear Image Registration Tool, Jenkinson et al., 2002). A spatial smoothing (gaussian kernel FWHM = 6 mm) and a high-pass temporal filter (cut-off = 100 s) were applied.

Functional images were linearly (FLIRT with BBR method, Boundary Based Registration, Greve and Fischl, 2009) registered to 3D T1-w volumetric images, and the latter were non-linearly warped to the MNI (Montreal Neurological Institute) template using FNIRT (Andersson et al., 2007) with a subsequent resample to $2 \times 2 \times 2\ mm^3$. Functional images could then be aligned to MNI space as well by combining these two transformations.

2.4. IC analysis

IC analysis was performed using a probabilistic approach as implemented in MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components 3.14 FSL tool, Smith,