FUNCTIONAL CONNECTIVITY IN NOCTURNAL FRONTAL LOBE EPILEPSY: AN FMRI RESTING STATE STUDY

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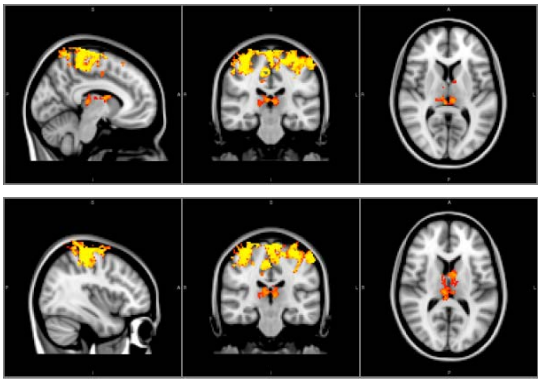
Target audience Neurologists and neuroradiologists interested in the physiopathology of nocturnal frontal lobe epilepsy (NFLE), within the framework of sleep disorders and motor parasomnias.

Purpose NFLE is characterized by seizures occurring predominantly or exclusively during sleep, mainly motor events, but with heterogeneus semiology, intensity and duration, and often bizarre[1,2]. The pathophysiology of the seizures has not yet been completely elucidated. Typically, conventional brain MRI shows no alterations. The purpose of this study was to evaluate fMRI resting state functional connectivity (rs-fc) in NFLE patients compared to healthy controls.

Methods Between April 2012 and October 2014, 13 patients with a clinical diagnosis of NFLE (age=38.3±11.8 years, 6M, disease duration=25.6±14.6 y, age at onset=12.6±6.9 y) and 13 sex matched healthy controls (age=38.5±10.8 y, 6M) underwent a standardized MRI protocol, including T1-weighted volumetric imaging (FSPGR, TR/TE=12ms/5ms, 1mm isotropic resolution) and two runs of resting state fMRI (axial GR-EPI, TR/TE=3000 ms/40 ms, 34 slices *per vol*., 90 vol. *per run,* spatial resolution=1.875x1.875x4 mm). Acquisitions were performed with a 1.5-T GE Signa scanner with an 8-channel head coil. Analyses were performed using probabilistic ICA as implemented by MELODIC 3.14 FSL tool. After visual identification of noise components on single-subject ICA and denoising, a temporally concatenated group ICA was performed, followed by dual regression (FSL/FMRIB, U Oxford) to generate subject-specific resting state network (RSN) maps, which then entered voxelwise group statistical comparisons performed using a nonparametric bootstrap method (FSL/FMRIB, U Oxford). To control for the effect of structural differences, individuals' modulated gray matter maps were included as voxelwise confounding regressors. Age was also added as a confounding regressor. Statistical significance was set at $p<0.05$ FWE-corrected for multiple comparisons with TFCE (Threshold-Free Cluster Enhancement).

Results NFLE patients showed greater functional connectivity relative to controls within a resting state network involving bilateral cortical and subcortical areas, in particular precuneus, superior parietal lobe, supplementary motor area, postcentral gyrus, precentral gyrus and thalamus (Figure and Table).



Brain area	Max intensity (1-p)	Volume (mm^3)	MNI coordinates maximum voxel		
			x	y	z
R Precuneous	0.9996	7984	42	37	71
L Precuneous	0.9992	7312	52	40	61
R Superior Parietal Lobule	0.9996	8392	38	37	70
L Superior Parietal Lobule	0.9996	7944	54	38	67
R SMA	0.9992	3616	43	57	72
L SMA	0.9992	4592	46	56	65
R Postcentral Gyrus	0.9996	18320	26	48	64
L Postcentral Gyrus	0.9996	21016	66	47	63
R Precentral Gyrus	0.9996	17712	27	51	68
L Precentral Gyrus	0.9996	19336	47	53	65
R Thalamus	0.9838	6128	42	48	41
L Thalamus	0.9812	6816	48	50	40

Figure - Areas of increased rs-fc in patients compared to controls, superimposed to the MNI-152T1 template.

Table - Brain areas showing a significantly increased rs-fc within the RSN. Coordinates are given in voxels, referred to the MNI space. Brain areas are based on the Harvard Oxford Atlas.

Discussion The thalamus is a primary structure involved in non-REM spindles and the generation of k-complexes[3]. Our results may suggest an alteration of the arousal regulatory system, with a particular excitability of the cortex during thalamic spindles and k-complexes. Especially for the genetic forms of NFLE, an effect of neuronal excitability on thalamo-cortical loop has been hypothesized[1]. NFLE is typically considered focal, even if some ictal manifestations can hardly be related to a single specific area, suggesting an involvement of wider brain networks[2]. Further in-depth analysis of resting state functional connectivity may improve comprehension of functional alterations in this disorder.

Conclusion The present study is to date the first undertaken of fMRI rs-fc in NFLE patients, and shows increased rs-fc in NFLE patients, compared to healthy controls, between thalamus and motor cortical areas; this finding may provide new insights into the physiopathology of the disease.

References

1. Nobili L, Proserpio P, Combi R, Provini F, Plazzi G, Bisulli F, Tassi L, Tinuper P. Nocturnal Frontal Lobe Epilepsy. Curr Neurol Neurosci Rep. 2014; 14:424.
2. Tinuper P, Bisulli F, Provini F, Montagna P, Lugaresi E. Nocturnal Frontal Lobe Epilepsy: New pathophysiological interpretations. Sleep Med. 2011; 12 (Suppl2): 39-42
3. Caporro M, Haneef Z, Yeh HJ, Lenartowicz A, Buttinelli C, Parvizi J, Stern JM. Functional MRI of sleep spindles and K-complexes. Clin. Neurophysiol. 2012; 123:303-309