Novel heterogeneity analysis of resting-state fluctuations in first-fit seizures and new-onset epilepsy

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Target Audience

Researchers and clinicians working in the area of the applications for epilepsy and functional Magnetic Resonance Imaging (fMRI).

Purpose

Epilepsy is defined by an enduring predisposition to generate epileptic seizures. Up to 10% of men worldwide have one seizure during their lifetime. However, one single seizure does only equal epilepsy after a recurrent seizure. What makes that patients with a first seizure will suffer from recurrent seizures is unknown. In analogy to electro-encephalographic assessment, temporal heterogeneity in blood-oxygen-level-dependent (BOLD) time-series might predict recurrent seizures. Therefore we compared resting-state fluctuations in patients with a first single epileptic seizure (first-fit) to patients with new-onset epilepsy and healthy controls. We used known heterogeneity measures, including fractional amplitude of low frequency fluctuations (fALFF)[1] and regional homogeneity (ReHo)[2] to evaluate the resting-state fMRI data.

Method

We included (adult) patients with a first single epileptic seizure (FF, first-fit, n=14), new-onset epilepsy (NOE, n=11) and healthy controls (HC, n=14). We used clinical criteria as a gold standard for the diagnosis of epileptic seizures and epilepsy. Resting-state fMRI data were acquired with a 3.0-Tesla unit (Achieva TX, Philips) using an echo-planar imaging (EPI) sequence with the following parameters: TR 2 s, TE 35 ms, Flip Angle 90°, 31 transverse slices, slice thickness 4 mm, and 195 volumes per acquisition. For anatomical reference, a fast gradient echo T1-weighted image set was acquired with the following parameters: TR 8.1 s, TE 3.7 ms, Flip Angle 8 °, 52 slices and 1 mm voxel size.

Using SPM8 software, the functional images were slice-time and motion corrected, co-registered to the anatomical template and smoothed with a kernel of 8 mm (full-width-at-half-maximum). Any signal drifts were corrected by removing the very low frequency components (<0.01 Hz). To correct for physiological fluctuations, the time-series from the cerebrospinal fluid (CSF) and white matter were included as co-variates in the linear regression analysis. Gray matter, white matter, and CSF voxels were segmented from the T1-weighted images using Freesurfer.

Continuous wavelet transform (CWT)[3] was applied to whole-brain time-series data to analyze the frequency and time responses of the three groups. CWT was also used to get an indication of the relevant frequency range for studying differences. The fALFF measures the strength of the BOLD fluctuations and was calculated for each gray matter voxel by dividing the amplitude of the BOLD signal in the specified frequency bands (low band: 0.02–0.09 and high band: 0.09-0.25 Hz) by the amplitude of the entire BOLD signal (0.01–0.25 Hz). ReHo measures the regional homogeneity (i.e. similarity in contiguous voxels) of time-series and was also averaged over all gray matter voxels. This method is based on observations that meaningful BOLD fluctuations are more likely to occur in clusters of several contiguous voxels than in a single voxel.

Results

Group averaged CWT coefficients are shown in figure 1. Note the prominent resting-state fluctuations in the low-frequency range (<0.09 Hz), especially for the HC, and the strong differences with the NOE, and to some extent also the FF, patients. In line with these observations, the CWT indicates that the standard deviations (SD) of FF and NOE were significantly lower than for HC. Heterogeneity measures are listed in table 1. For the low band, the fALFF was significantly lower for FF than for NOE and HC, but not for the high band. The ReHo, for both bands, the NOE, and a trend for the FF, patients were lower in comparison to the HC.

Discussion

Patients with new-onset epilepsy or a first-fit seizure reveal increasing temporal heterogeneity (i.e. decreased fALFF and ReHo) in their low-frequency dynamic BOLD fluctuations. In particular for this low frequency range, 0.02-0.09 Hz, results suggest that especially NOE, but also FF, patients have attenuated BOLD fluctuations. These effects show that the use of frequency fluctuations has potential to contribute to the prediction which patients have an increased risk to develop epilepsy after a single seizure.

To further optimize the sensitivity of the analysis methods, more subjects may be needed and more detailed analysis is required into specific brain regions, possibly mediating the seizures. The current data set may serve as a training data set to use for a diagnostic prediction evaluation when the course of seizures in FF patients becomes available.

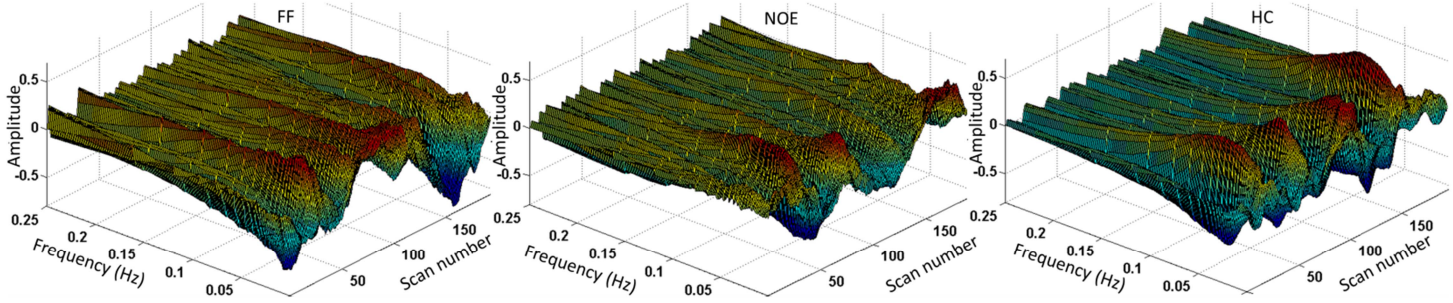

Figure 1: CWT coefficients for first-fit patients (FF), new-onset epilepsy patients (NOE) and healthy controls (HC).

Table 1: Heterogeneity measures

Quantity	Mean ± standard error			*p*-value (Wilcoxon rank-sum test)		
	FF	NOE	HC	FF vs NOE	NOE vs HC	FF vs HC
CWT SD (0.02-0.09 Hz)	0.562±0.184	0.486±0.069	0.953±0.155	0.44	0.05	0.04
fALFF (0.02-0.09 Hz)	0.239±0.003	0.252±0.004	0.285±0.006	<0.01	<0.01	<0.01
fALFF (0.09-0.25 Hz)	0.531±0.009	0.519±0.006	0.529±0.008	0.09	<0.01	<0.01
ReHo (0.02-0.09 Hz)	0.106±0.006	0.124±0.009	0.156±0.006	0.06	<0.01	<0.01
ReHo (0.09-0.25 Hz)	0.092±0.008	0.116±0.009	0.154±0.005	0.08	<0.01	<0.01

References:

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