# Simultaneous EEG-fMRI in patients with Unverricht-Lundborg disease: event-related desynchronization/synchronization (ERD/ERS) and haemodynamic response analysis

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***Abstract***. We performed simultaneous acquisition of EEG-fMRI in a group of patients with Unverricht–Lundborg disease (ULD) using self-paced finger extension as a motor task. We analyzed the movement-related ERD/ERS in α and β frequency bands in 7 patients, and compared the results with those obtained in 6 healthy volunteers. Furthermore, we report results from event-related analysis of the hemodynamic response.

*Keywords:* ERD/ERS analysis, simultaneous EEG-fMRI, progressive myoclonic epilepsy

## 1. Introduction

The analysis of the EEG recorded during motor performance (self-paced movement) provides information about the movement-related changes in oscillatory cortical activity. In normal subjects, an amplitude attenuation of specific frequency components (event-related desynchronization, ERD) in the α- and β-bands precedes a voluntary movement, and reflects cortical activation concurring with movement planning. At the end of the movement, event-related synchronization (ERS) in the β-band replaces ERD [Pfurtscheller and Lopes da Silva, 1999]. Simultaneous EEG-fMRI acquisition during performance of a motor task enables the identification of changes in brain activity in motor areas, and provides information on the source of the event generator.

In Unverricht-Lundborg disease (ULD) patients, voluntary movements are selectively impaired by the presence of action myoclonus [Koskiniemi et al., 1974]. In these patients, ERD/ERS changes highlight increased and diffuse activation of the motor cortex during movement planning, and severely reduced post-excitatory inhibition of the motor cortex [Visani et al., 2006].

We simultaneously acquired EEG and fMRI in order to study the spatiotemporal pattern of ERD/ERS resulting from self-paced extension of the index finger in ULD patients, and to explore the correlation with hemodynamic changes.

## 2. Material and Methods

We enrolled 7 right-handed patients (mean age: 29.1±10 years; four women) with ULD, whose main clinical features are reported in Table 1, and 6 right-handed healthy controls (mean age: 29.1±6.7 years; five women). In all patients, the diagnosis of ULD was established on the basis the typical electroclinical presentation, and of the genetic finding of dodecamer expansion at *cstb* gene [Virtaneva et al., 1997].

### 2.1. Motor task

Inside the bore of the scanner, subjects laid supine with their arms relaxed; their head was stabilized with adjustable padded restraints on both sides. They were instructed to remain as still as possible throughout the experiment, to keep their eyes open and avoid blinking during the task. Subjects were asked to perform brisk (i.e., lasting less than one second) self-paced extensions of the right index, with a time interval between the end of a movement and the onset of the following one of about 10 s. Each subject was trained for several minutes before the experiment. The movement was monitored by electromyography (EMG) and visual observation.

***Table 1.*** *Patient data*

| *Subject, Age [yrs], Sex* | *Disease duration [yrs]* | *AED* | *Simplified myoclonus rating* |
|---|---|---|---|
| 1, 22, f | 12 | VPA, TPM, CLZ | 2 |
| 2, 26, f | 16 | VPA, CZP | 2 |
| 3, 36, m | 22 | VPA, LVT, PB | 2 |
| 4, 25, m | 14 | VPA, CZP, piracetam | 3 |
| 5, 49, m | 34 | VPA, TPM | 2 |
| 6, 22, f | 11 | VPA, LVT, TPM | 2 |
| 7, 24, f | 12 | VPA | 3 |

Legend: AED=anti-epileptic drugs; VPA=valproate; TPM=topiramate; CLZ=clobazam; CZP=clonazepam LVT=levetiracetam; PB=phenobarbital. Simplified myoclonous rating [*Magaudda et al., 2004*]: 2=mild myoclonous, interference with fine movements and/or speech, no interference with walking; 3=moderate myoclonous, patient still able to walk without support

### 2.2. EEG-fMRI acquisition

EEG was acquired using a MR compatible EEG amplifier (SD MRI 32, Micromed, Treviso, Italy) and a cap providing 30 Ag/AgCl electrodes positioned according to the 10/20 system. Impedance was kept below 5 kΩ. Electrocardiogram (ECG) and EMG were simultaneously recorded. The EMG activity was recorded from pairs of Ag/AgCl surface electrodes placed bilaterally 2–3 cm apart over the right index flexor muscles. EEG data were acquired at the rate of 1024 Hz using the SystemPlusEvolution software package provided by the manufacturer.

Imaging was performed on a 1.5 T MR scanner (Magnetom Avanto, Siemens AG, Erlangen, Germany). Functional images were acquired with an axial gradient-echo echo-planar sequence (21 slices, TR = 2000 ms, TE = 50 ms, 2x2 $mm^2$ in-plane voxel size, 5 mm slice thickness, no gap). A $T_1$-weighted anatomical scan (160 slices, TR = 1640 ms, TE = 2 ms; 1 $mm^3$ isotropic voxels) was also acquired.

The scanner provided a trigger signal corresponding to the excitation of the first slice of each volume, which was recorded by the EEG system enabling real-time artefact removal, making it possible to monitor the EEG signal as well as task performance through EMG.

### 2.3. Data analysis

The imaging gradient artefact and the ballistocardiogram (BCG) were digitally removed from the EEG using an adaptive filter, implemented on software provided by the manufacturer.

Movement onset was determined by the beginning of the burst of EMG activity. EEG data were epoched four seconds before and three seconds after movement onset. Epochs with artefacts, incomplete muscle relaxation between movements, and inter-trial interval shorter than 8 s were excluded from the analysis. A reference period at rest, from 3500 to 2500 ms before movement onset, was considered. Each trial was digitally band-pass filtered from 1 Hz below to 1 Hz above the individual frequencies of the most movement-sensitive power peaks in α- and β-bands. The filtered EEG data were then squared and averaged over all trials and over time (one value every 125 ms). The ERD or ERS values were calculated according to the following formula:

$$ERD\%(k) = \frac{A(k) - R}{R} \times 100$$

where

A(k)=power at sample k

R=mean power of the reference period

The statistical significance of the differences between the mean power observed during the reference period and that measured during the subsequent 125-ms intervals was expressed as a probability value using Wilcoxon's signed rank test. The power changes were considered significant when the p value was less than 0.05. ERD/ERS data analysis was performed using software developed in Matlab (Mathworks Inc., Natick, MA, USA). For statistical analysis, we divided the time course of ERD/ERS in five epochs of 1 second each (t1: -2.5 to -1.5 s, t2: -1.5 to -0.5 s, t3: -0.5 to 0.5 s, t4: 0.5 to 1.5 s, t5: 1.5 to 2.5 s) and we compared the values measured on F4, C4, P4, F3, C3, P3, Fz, Cz and Pz electrodes.

The fMRI data were analyzed by means of the SPM5 software (Wellcome Neuroimaging Dept., Institute of Neurology, London, UK). Preprocessing included three-dimensional motion correction, slice-timing correction, Gaussian smoothing and normalization into MNI (Montreal Neurological Institute) space. First-level analysis was performed by general linear model (GLM), using the event function from EMG, convolved with the canonical haemodynamic response function, as regressor Three-dimensional regions of interest (ROIs) were manually drawn for each subject by an experienced operator on the contralateral and ipsilateral primary motor areas, as well as on the contralateral supplementary motor area. The average signal time-course was obtained, and the amplitude and latency of the peak of the fitted haemodynamic response were measured.

For statistical analysis, the Mann–Whitney U test was applied.

## 3. Results

All subjects performed task well: the mean movement duration was on average longer in the patients group (535.8±110.3 vs 728.6±195.5 ms; p=0.062). The α- and β- band peak frequencies, selected as movement reactive EEG frequency, were lower in the patient group with respect to controls and in α-band this difference reached statistical significance (α: 11.3±0.8 vs 9.1±1.6 Hz, p=0.02; β: 22±5.6 vs 18.6±1.5 Hz).

### 3.1. ERD/ERS analysis

In all subjects α- and β-ERD was observed. The time course of the α- and β-desynchronization was similar for the two groups, but in patients the desynchronization in the α-band was significantly greater in central and parietal regions (*Table 2* and *Figure 1*).

The expected post-movement β-ERS was observed in all controls; it was undetectable in two patients, whereas in the remaining patients the β-peak was significantly smaller with respect to that measured in controls (107.5±86.9 vs 31.3±8.8; p=0.025, for controls and patients respectively, *Table 2* and *Figure 2*).

***Table 2.*** *Statistical analysis of ERD/ERS time course*

| ***Alpha band*** | ***F4*** | ***C4*** | ***P4*** | ***F3*** | ***C3*** | ***P3*** | ***Fz*** | ***Cz*** | ***Pz*** |
|---|---|---|---|---|---|---|---|---|---|
| t1 | - | 0.015 | - | - | - | - | - | 0.032 | - |
| t2 | - | 0.010 | - | - | - | 0.042 | - | - | - |
| t3 | - | 0.003 | - | - | - | - | - | 0.003 | - |
| t4 | 0.045 | 0.010 | - | - | 0.015 | 0.004 | 0.007 | 0.003 | 0.032 |
| t5 | - | - | - | - | - | - | - | 0.007 | - |
| ***Beta band*** | ***F4*** | ***C4*** | ***P4*** | ***F3*** | ***C3*** | ***P3*** | ***Fz*** | ***Cz*** | ***Pz*** |
| t1 | - | - | - | - | - | - | - | - | - |
| t2 | - | - | - | - | - | - | - | - | - |
| t3 | - | - | - | - | - | - | - | - | - |
| t4 | 0.032 | - | 0.007 | - | 0.032 | - | 0.015 | - | - |
| t5 | - | 0.032 | 0.022 | - | 0.012 | - | - | 0.010 | - |

Results of U-Mann Whitney test between patients and controls group. -=not significant

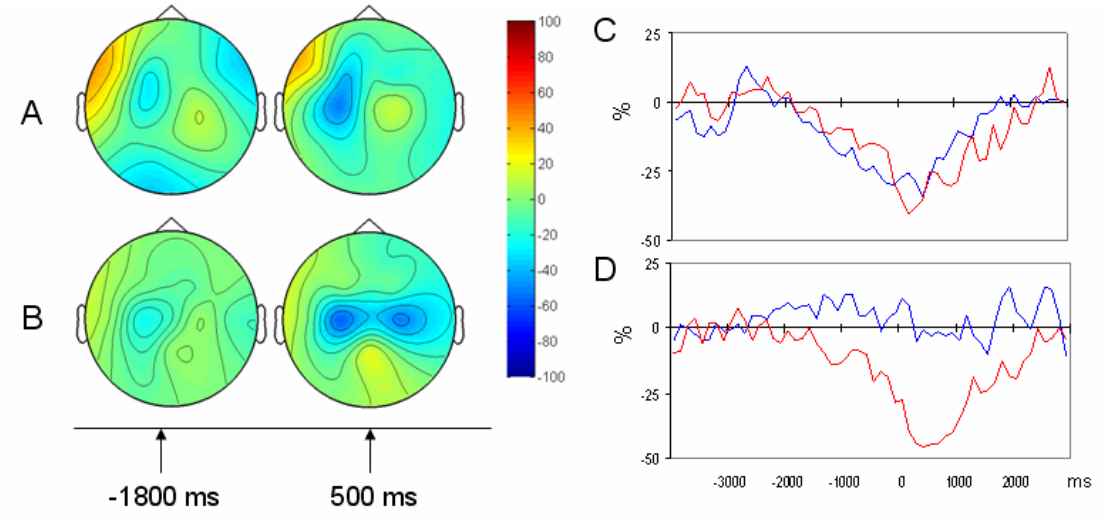


***Figure 1.*** α-ERD color maps for a control subject (A) and a representative patient (B). Grand average of the time series of α-ERD in patients and controls recorded from contralateral (C) and ipsilateral (D) central derivations .

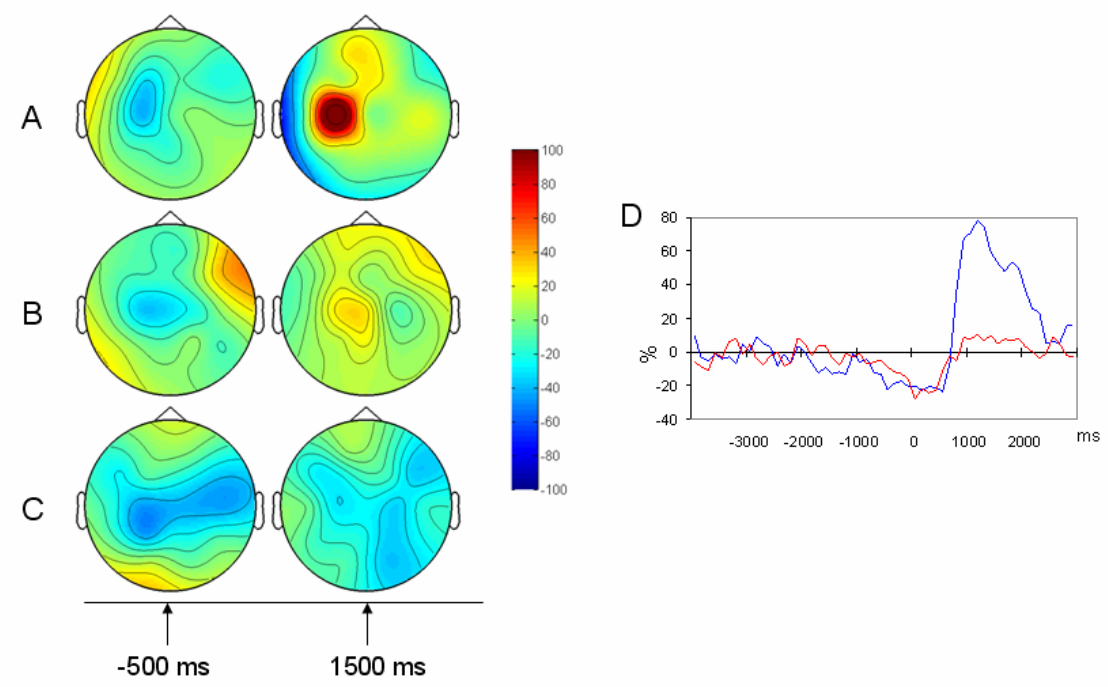


***Figure 2.*** β-ERD/ERS color maps in a control subject (A) and in two representative patients (B,C). Grand average of the time series of β-ERD/ERS in patients and controls recorded from contralateral central derivations (D).

### 3.2. fMRI analysis

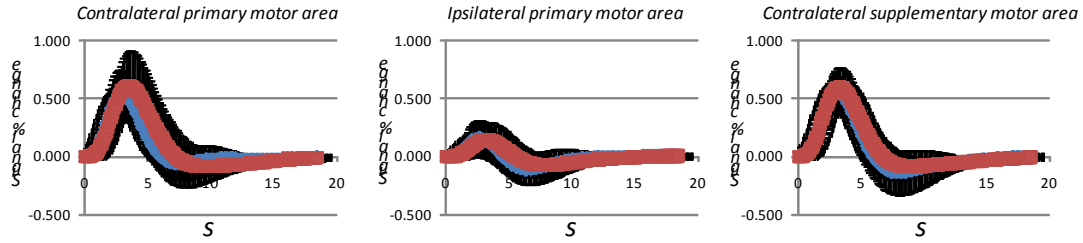


***Figure 3.*** Time-courses of the haemodynamic response for controls (blue) and patients (red).

The peak amplitude of the haemodynamic response was comparable for controls and patients in the contralateral (0.56±0.18% vs. 0.63±0.30%, p=0.6) and ipsilateral (0.17±0.15% vs.0.17±0.14%, p=0.8) motor areas, as well as in the contralateral supplementary motor area (0.58±0.15% vs. 0.60±0.17%, p=0.8).

There was, however, a trend towards longer response latency in patients, which reached statistical significance in the contralateral motor area (3.1±0.4 s vs. 3.6±0.5 s, p=0.011) and approached statistical significance in the contralateral supplementary motor area (3.1±0.4 s vs. 3.4±0.2 s, p=0.08); the effect was not found in the ipsilateral motor area (2.7±0.2 s vs. 3.3±0.8 s, p=0.1).

## 4. Discussion and conclusions

The consistent changes found in ERD/ERS pattern of ULD subjects indicate an increased activation of motor cortex during movement planning and a great reduction of post-excitatory inhibition of motor. These data completely overlaps those obtained in our previous study [Visani et al., 2006] on EEG signal obtained in standard EEG laboratory.

In spite of the fact that significant differences were identified with ERD/ERS, fMRI did not highlight any effect on these patients. The very small number of participants limits statistical power and prevents from reaching final conclusions. Major differences in the level of neurovascular engagement of the motor cortices seem to be absent, but there may be more subtle effects on the time course of activation. Elevated response latency may, in fact, be a direct correlate of longer movement duration in patients. If confirmed, a dissociation between ERD/ERS and event-related fMRI findings could potentially be interpreted as indicating that ERD/ERS changes are more representative of an altered pattern of interaction among multiple cortical areas, rather than of specific, local dysfunction in the motor cortex. Further analyses exploring the functional connectivity during performance of this task are called for.


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