

EEG–EMG Information Flow in Movement-Activated Myoclonus in Patients with Progressive Myoclonic Epilepsies

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Abstract. We aimed this study at verifying the appropriateness of generalized partial directed coherence (GPDC) in detecting EEG–EMG information flow and identifying the characteristics of myoclonus-related EEG changes in patients with progressive myoclonus epilepsy (PME). Our results indicate that GPDC analysis is able to detect the presence of a different pattern of connectivity between the EMG and sensorimotor EEG derivations in all patients, namely a larger and more extensive flow of information in beta band coming out from the cortex and driving the muscular activity in patients with respect to controls.

Keywords: GPDC, MVAR, cortical myoclonus, EEG, epilepsy.

1. Introduction

After the earliest demonstration of synchronisation between muscles and cortical activities in 1990s [Farmer et al., 1993], spectral analysis became an important tool to investigate the human motor system. In the last decade, spectral analysis, namely coherence and phase analysis, based on Fast Fourier Transform (FFT) [Brown et al., 1999; Grosse et al., 2003] or autoregressive (AR) models [Panzica et al., 2003; Panzica et al., 2010] has been increasingly applied as an alternative method to jerk-locked back-averaging (JLBA) [Shibasaki and Kuroiwa, 1975] for investigating the relationship between rhythmic or quasi-rhythmic myoclonic events and EEG oscillations. Myoclonus can result from different neurological dysfunctions, presenting as sudden, brief, shock-like, involuntary movement caused by muscular contractions (or inhibitions). The diagnostic definition of cortical myoclonus is usually based on the presence of cortical correlates that are often difficult to detect.

Studies investigating the EEG changes associated with cortical myoclonus indicated that significantly coherent beta activities occur in the motor cortex and muscles during cortical myoclonus. In this frequency range, often the phase difference between the EEG and EMG signals was compatible with direct corticomuscular conduction time between motor cortex and muscle, according to conduction measures performed by means of transcranial magnetic stimulation (TMS), thus suggesting a cortical origin of myoclonus. However, sometimes, the phase difference indicated a time lag that is lower than expected for the fastest conducting pathway. This phenomenon may be due to the presence of multidirectional activities that contributed to the cortico-muscular coherence between muscle and cortex (efferent control from the primary motor cortex to muscle and afferent feedback from the periphery) with differing phase relationships. Moreover, contribution from other cortical regions or from volume conduction effect cannot be excluded. Alternative methods based on multivariate autoregressive (MVAR) modeling together with the concept of Granger causality can be used to evaluate the existence and direction of causal influences among multiple time series.

We aimed the present study at verifying the appropriateness of generalized partial directed coherence (GPDC) [Baccalà and Sameshima, 2001] in detecting EEG–EMG information flow and

identifying the characteristics of myoclonus-related EEG changes in patients with progressive myoclonus epilepsy (PME).

GPDC is based on multivariate AR models that provide a multivariate representation of polygraphic signals, from which appropriate measures of coupling can be estimated. The main advantages of GPDC with respect to other measures is that it allows the estimation of the direction of information flow between any two channels by subtracting the interactions and possible common influences due to other remaining simultaneously observed time series.

2. Material and Methods

PMEs are complex neurological disorders resulting from different genetic defects and leading to multifocal and massive myoclonic jerks associated with seizures and other neurological symptoms (including mild ataxia and a variable degree of mental decline). Among the population of patients with PME observed at the Department of Neurophysiology of the IRCCS Foundation C. Besta Neurological Institute, we selected 8 patients with Unverricht-Lundborg disease (ULD). In this disorder, myoclonus is the more severe and invalidating symptom, while the mental decline is mild or absent. Moreover, the study involved 8 healthy volunteers as controls.

2.1. Polygraphic recordings: EEG was recorded by means of Ag/AgCl surface electrodes placed on the scalp according to the 10–20 International System; surface EMG signals were simultaneously recorded from pairs of electrodes placed bilaterally 2–3 cm apart over the belly of the flexor and extensor wrist muscles. The recordings were obtained at rest and during simple voluntary motor activities (left and right hand extension, lasting at least two minute each). The EEG and EMG signals were acquired at a sampling frequency of 256 Hz (band pass filters 1.6–120 Hz).

2.2. Connectivity analysis: The presence of artefacts on the EEG signals due to physiological or non-physiological sources was accurately checked by an expert neurophysiologist, and epochs contaminated by any type of artefacts were excluded from the analysis. As a pre-processing step, the signals were normalised by subtracting the mean value and dividing by the standard deviation and a spline Laplacian was applied to EEG channels to ensure reference-free and spatially sharpened data [Perrin et al., 1989; Babiloni et al., 2004]. Afterwards, one minute of EEG and EMG signals were segmented into non-overlapping 2 s epochs for the analysis. We considered these epochs as multiple realizations of the same process and thus we computed GPDC for each realization and then averaged them across all the realizations to obtain the final estimate.

Given a set $S = \{x_m(k), 1 \leq m \leq M\}$ of M simultaneously observed stationary time series, the multivariate autoregressive (MVAR) model with order p is defined as

$$\begin{bmatrix} x_1(k) \\ \vdots \\ x_M(k) \end{bmatrix} = \sum_{r=1}^p A_r \begin{bmatrix} x_1(k-r) \\ \vdots \\ x_M(k-r) \end{bmatrix} + \begin{bmatrix} w_1(k) \\ \vdots \\ w_M(k) \end{bmatrix} \quad (1)$$

where A_1, A_2, \dots, A_p are the coefficient matrices (dimensions $M \times M$), with the coefficient $a_{ij}(r)$ describing the linear interaction of $x_j(k-r)$ on $x_i(k)$, and $w_i(k)$ represents a random (Gaussian) white noise driving innovation. The model order was determined using the multichannel version of the Akaike (AIC) criterion as a guideline. The goodness of the identification was verified by means of ‘portmanteau’ chi-square and Anderson’s tests [Box and Jenkins, 1970]. The multivariate time series for the MVAR modelling included the signals from the sensorimotor areas (F4,C4,P4, F3,C3,P3) that are critically involved in the generation of myoclonic jerks and EMG from the right or left wrist extensor.

Once the MVAR coefficients had been adequately estimated, the GPDC from channel j to i (π_{ij}) was calculated from the Fourier transform of the MVAR coefficients as:

$$|\pi_{ij}(f)| = \frac{\frac{1}{\sigma_i} |\bar{A}_{ij}(f)|}{\sqrt{\sum_{k=1}^p \frac{1}{\sigma_k^2} |\bar{A}_{k,j}(f)|^2}} \quad (2)$$

Where σ_i refers to the variances of the innovation processes, and

$$\bar{A}(f) = I - \sum_{r=1}^p A_r e^{-2i\pi\Delta t f r} \quad (3)$$

Δt is the sampling interval and I is the identity matrix of dimension $M \times M$.

The GPDC from j to i , describes the directional flow of information from signal $x_j(t)$ to $x_i(t)$. PDC values range between 0 and 1, and represent the fraction of the time evolution of the j^{th} signal directed towards the i^{th} signal, in comparison with all of j 's interactions with all the other channels.

In order to assess the statistical significance of non-zero PDC values at each frequency, a bootstrap approach using phase randomisation [Zoubir and Iskander, 2004] was applied on the basis of Theiler' method [Theiler et al., 1992].

Only the significant flows outgoing from EEG and directed towards EMG signal was considered for the analysis. GPDC peaks values and areas (integration of GPDC across the significant frequencies) in the beta band was calculated and statistically analyzed by Mann-Whitney U test.

All data analysis were performed using custom written routines in the Matlab environment (Version 7.13, R2011b; Mathworks Inc., USA).

3. Results

In UL patients, the active movements typically elicited irregular bursts of myoclonic jerks intermingled with short segments of tonic muscle contraction (Fig. 1), or short rhythmic sequences at variable frequencies.

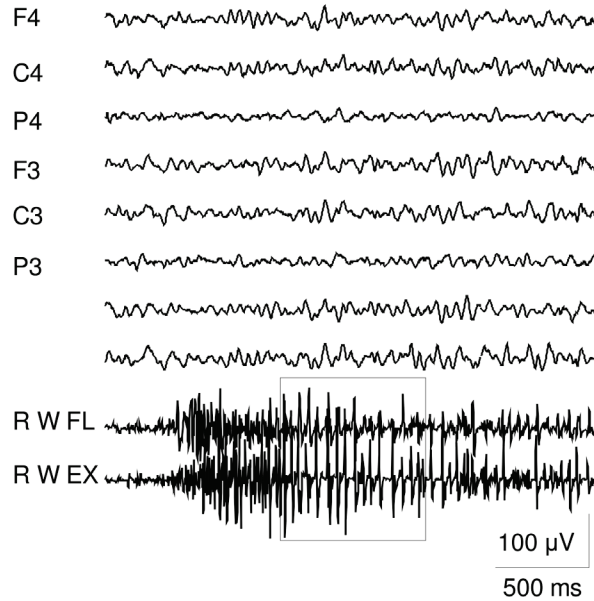


Figure 1. Representative example of movement-activated myoclonus during voluntary right hand extension in a ULD patient. Myoclonic jerks are evident on the antagonist muscle couple (right wrist flexor and extensor)

Significant cortico-muscular GPDC in beta band was observed over the contralateral central derivation in all patients and in six out of the eight controls. Furthermore, the patients were characterized by the presence of significant additional outflow from other cerebral regions, contralateral (in all of the cases) and ipsilateral (in six) to the activated segment (Fig. 2 and 3).

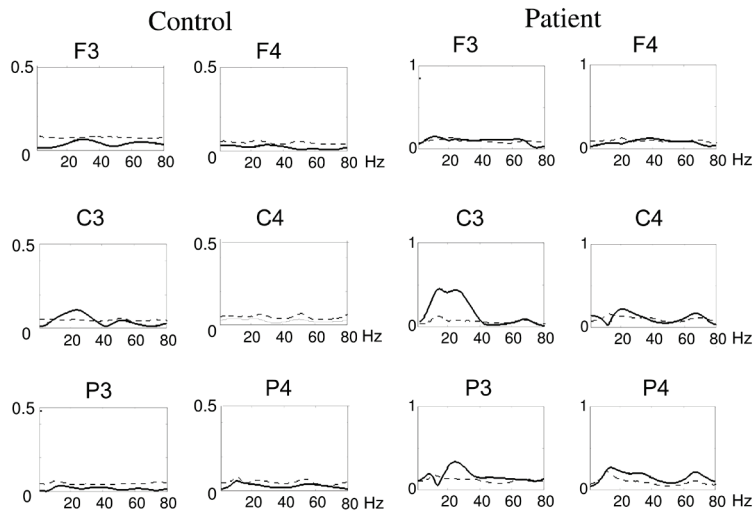


Figure 2. GPDC spectra showing the outflow from sensorimotor derivations towards muscle during right wrist extension. The dashed line indicates the 95% confidence level for the null hypothesis

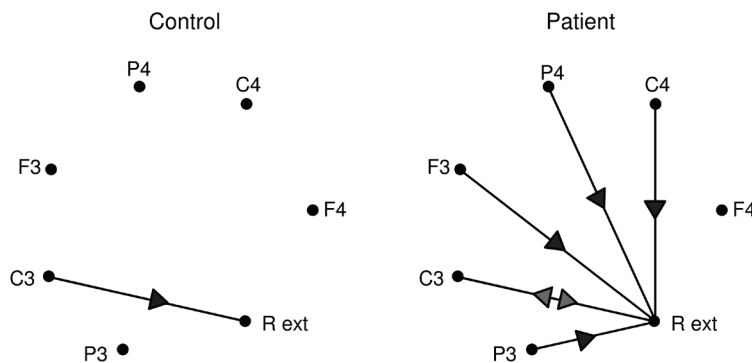


Figure 3. Outflow from cerebral regions towards muscle in beta band, for the same subjects reported in Fig. 2. Note also the ascending flow from muscle to the contralateral central cortex (C3).

The peak frequency was slightly higher in ULD patients than in controls (21.2 ± 4.2 and 20.0 ± 5.4 Hz) but the difference was not significant. Moreover, we did not find any significant difference in peak GPDC amplitude. On the contrary, the area subtended to GPDC curve over the contralateral central region in beta band was significantly larger in ULD patients than in controls ($p=0.033$, mean rank 9.69 and 4.58 respectively). The difference between ULD patients and controls was even larger taking into consideration the total outflow from cortex to muscle, that is the sum of the significant areas over all the electrodes (4.25 ± 3.6 versus 0.62 ± 0.058 ; $p=0.007$, mean rank 10.13 versus 4.00).

In six out of eight ULD patients, a significant causal influence in the ascending direction (from periphery to the contralateral sensorimotor region; see Fig. 3) was also observed. In two patients of this subgroup, the feedback was directed also towards the central area ipsilateral with respect to the activated segment.

4. Discussion

Our results indicate that MVAR models and GPDC appear to be a powerful tool capable of revealing and studying the oscillatory EEG activities associated with rhythmic or quasi-rhythmic

myoclonic discharges. With respect to other methods applied to evaluate cortico-muscular coupling (JLBA and coherence analysis between the EEG signal recorded by individual electrodes and EMG signals [Brown et al., 1999, Panzica et al., 2003, Shibasaki and Kuroiwa, 1975]), GPDC allowed the evaluation of multiple interactions between EEG oscillations and pathological EMG contraction.

Indeed, PME patients, differently from healthy subjects, had obviously outflow from cerebral regions other than the motor area contralateral to the activated muscle. This suggests that the abnormal connectivity pattern might originate from a widespread cortical hyperexcitability [Visani et al., 2006].

The evaluation of multiple interaction occurring during cortical myoclonus and other movement disorders may help in understanding the mechanism of generation within a complex network exceeding the motor cortex. Moreover GPDC was capable of revealing not only cortical outflow influences, accounting for the myoclonic jerks, but also inflow influences directed from the periphery towards the cortical areas. This method can therefore allow to overcome problems of bi-directional interactions between cortex and pathologically activated muscle, that cannot be captured by other methods.

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