Coherence and Phase Locking Disruption in Electromyograms of Patients with Amyotrophic Lateral Sclerosis

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Abstract: In motor neuron disease, the aim of therapy is to prevent or slow neuronal degeneration and early diagnosis is thus essential. Hypothesising that beta-band (15−30 Hz) is a measure of pathways integrity as shown in literature, coherence and phase locking factor (PLF) could be used as an electrophysiological indicator of upper and lower neuron integrity in patients with amyotrophic lateral sclerosis (ALS). In this work are applied such tools in different variable situations. Coherence and PLF analysis was computed for EMG signals registered from 2 groups: control subjects and ALS patients. The data was recorded during instants of steady contraction for both contra and ipsilateral acquisitions. Ipsilateral coherence and PLF was computed for one member of each group and results present significant differences between both groups. Contrarily, contralateral acquisitions were performed on 6 members of each group and both coherence and PLF results present no significant differences. So, while control subjects present no neuronal or muscular disorders and therefore higher synchrony and coherence for beta-band EMG signals, patients with ALS do not present synchronism or coherence in any frequency, specially for beta-band. All results allowed to conclude that contralateral coherence is not a good measure of corticospinal pathways integrity. However, ipsilateral acquisitions show promising results and it is possible to affirm that ipsilateral measurements may reflect neuronal degeneration. For future work is suggested a deeper analysis of PLF, that appear to have potential as a quantitative test of upper and lower neuron integrity related to ALS.

1 INTRODUCTION

Amyotrophic lateral sclerosis, one of the major neurodegenerative diseases, is a progressive incurable motor neuron disorder, fatal in all cases. Associated therapy involves slowing down or even preventing neuronal degeneration. Since the effectiveness of this medication depends on an early diagnosis, many efforts have been made to find accurate indicators of this disease. As a general rule, patients with ALS are diagnosed when there is already extensive motor neuron degeneration present, since the diagnosis is hampered by the impossibility to access the corticospinal tract.

Some motor cortex cells are capable of synchronizing their discharge with local oscillations in a 15−30 Hz range of frequency, known as beta-band. This synchronism happens during rest or steady con-

traction but is not common during movement. Despite all the research on this subject, there is no agreement on which function might induce such periodic activity (Baker et al., 2006). Some oscillatory cortical activity involves pyramidal neurones and is reflected in the descending drive to the muscles, being distributed to agonist and antagonist muscles, which can be observed in the EMG of these muscle pairs through coherence in beta-band (Cordivari et al., 2002). Corticomuscular coherence measures contributions from both ascending and descending pathways, which was proved by phase analysis, suggest that muscles led the cortical recordings (de Carvalho, 2012). The timing of synchronism is dependent on the intrinsic properties of the inhibitory interneurons and their conduction delay (Jackson et al., 2004). In both upper and down motor neuron disease, the focus is to prevent, if possible, or slow neuronal degeneration. Based on the

hypothesize that beta-band coherence could be used as an indicator of neuronal integrity, the aim of this work is to obtain coherence values averaged for each population and evaluate if significant differences were present between them. Therefore, find a way of an early diagnose for ALS, resorting to contra or ipsilalateral acquisitions.

1.1 Amyotrophic Lateral Sclerosis

This pathology is one of the major neurodegenerative diseases, a progressive disorder that involves widespread degeneration of the motor system neurons. Regions affected undergo destruction of layer V pyramidal neurons from the motor cortex to the anterior horn of the spinal cord. To diagnose such a disease it is necessary to find upper and lower motor neuron degeneration in multiple regions: bulbar, cervical, thoracic and lumbar. This disorder is characterized by the neurological regions affected, but there are common features observed in all patients such as a rapidly progressive weakness, muscle atrophy, muscle cramps, fasciculations, muscle spasticity, difficulties in breathing (dysponea), difficulties in swallowing (dysphagia) and difficulties in speaking (dysarthria). Patients tend to lose their abilities to control voluntary movements and symptoms tend to greatly reduce their quality of life (Kiernan et al., 2011).

1.2 Electromyography and Beta-band

Voluntary movement is associated with the presence of rhythmic activity in motor cortex. Beta-band, comprising a range of frequencies from 15 to 30 Hz, appears to vary its magnitude prior and during voluntary movements and is associated with the attempt to perform certain tasks (Halliday et al., 1998). In this same frequency band, cortical activity and motor unit firing are correlated during sustained voluntary contractions. Intermuscular coherence (EMG - EMG) between different muscle groups appears to detect characteristics of the same rhythmic processes, suggesting a common drive from corticospinal pathways. The precise function and genesis of these same cortical oscillations still remains elusive (Marsden et al., 2000). Motor units from muscle pairs can be modulated by a descending 15 - 30 Hz drive. So, this frequency band oscillations are mediated via corticospinal pathways, originating from sensorimotor cortex and are coherent with muscles (Marsden et al., 2000; Nishimura et al., 2009). These oscillations may arise in motor systems in order to promote synchronous neuronal firing between neurons populations that are spatially distributed but functionally related, providing means of linking different neuronal populations (Marsden et al., 2000). Coherent activity may represent a common element in coding activity in simultaneous active motor centres. Cortical areas involved in the same motor task may be coherent with each other. Active muscles show coherence around beta-band, reflecting the activity of neuronal structures involved in driving the spinal motoneurons (Nishimura et al., 2009). Coherence has demonstrated that some of these oscillations are probably transmitted via pyramidal tract to activate muscles and may induce the same rhythm on them (Nishimura et al., 2009).

1.3 Coherence

Coherence analysis of motor unit firing behaviour can provide information about the organization of networks responsible for driving spinal motoneurons during task performance. It also assesses common presynaptic inputs that synchronize motor units populations. In the human body, different activities may be characterized by functional activities in distinct circuits, due to muscles discharges at a certain frequency. Some of these oscillating frequencies let to spinal motoneurones (Grosse et al., 2002). Coherence is a measure of the linear correlation between the frequencies presented in two signals, being usually computed using discrete Fourier transforms. As a function of frequency (λ), for the rectified x and y signals, auto spectra $f_{x,x}(\lambda)$, $f_{y,y}(\lambda)$ and cross spectra $f_{x,y}(\lambda)$ are calculated to assess measures of correlation (Farmer et al., 2007; Grosse et al., 2004). Cross-correlation is assessed by coherence function - $|R_{x,y}(\lambda)|^2$ - defined as the squared magnitude of cross spectrum, normalized by the product of the two auto spectra as show in equation 1.

$$|R_{x,y}(\lambda)|^2 = \frac{|f_{x,y}(\lambda)|^2}{|f_{x,x}(\lambda)f_{y,y}(\lambda)|} \qquad (1)$$

1.4 Phase Locking Factor

During oscillatory activity, neurons fire synchronously. Therefore, common target cells will receive neural activity synchronously and so, oscillations play an important role for the timing of neural activity (Klimesch et al., 2008). On the assumption that coherence between two signals exists for beta-band, it would be interesting to investigate if both signals are synchronized within this frequency range. I.e. if the phase difference between the signals is kept constant. To evaluate such behaviour, one can determine the phase locking factor between both

signals, using Hilbert transforms. For signals x and y, $\phi_x(t)$ and $\phi_y(t)$ represent signals phase dependency on time, respectively, for $t = 1, ..., T$. PLF between both signals is defined by (Almeida et al., 2011):

$$\rho_{xy} \equiv |\frac{1}{T}\sum_{t=1}^{T} e^{i[\phi_{jx}(t)-\phi_y(t)]}| = |\langle e^{i[\phi_x(t)-\phi_y(t)]}\rangle| \quad (2)$$

PLF assumes values from 0 to 1. 0 stands for signals entirely asynchronous, with phases randomly distributed; 1 stands for signals perfectly synchronized and with a constant phase lag. Values between 0 and 1 represent partial synchrony. To perform the PLF computation it is necessary to isolate the frequencies of interest, applying a band-pass filter with a narrow band centred on each value of frequency in study.

2 ACQUISITIONS

2.1 Subjects

Focussing on previous published results (Fisher et al., 2012), ipsilateral measurements were performed on 1 member from the group of patients and 1 member from the group of control. Contralateral measurements required the existence of two different groups of subjects: group of 6 patients presenting ALS and a control group of 6 subjects. All participants from the control group do not present any known neuronal or muscular disease, whereas patients with ALS had been diagnosed within less than one year. For patients with ALS that were in a more advanced stage of the disease, presenting more difficulties that limited their own movement control, it was impossible to collect an analysable EMG signal.

2.2 Recordings

For each ipsilateral acquisition, two signals were simultaneously acquired from each subject using EMG sensors attached to a bioPlux device, as observed in figure 1. For both right and left hand, signals were collected using two sensors attached to first dorsal interosseus muscle; for both right and left forearm, signals were collected using two sensors attached to extensor digitorum communis muscle. Ground was placed in ulna bone inferior extremity, where no muscle activity is present.

For each contralateral measurement, two signals were simultaneously acquired from each subject, using two EMG sensors attached to a bioPlux device. Each sensor (one for each hand) has two connected
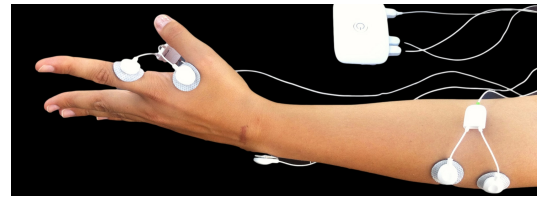

Figure 1: Ipsilateral acquisitions experimental setup for left member: Bioplux research device, placement of two EMG sensors and ground.

Figure 2: Contralateral acquisitions experimental setup: Bioplux research device, placement of two EMG sensors and ground.

electrodes placed in first dorsal interosseus muscle. Ground was placed as in ipsilateral recordings. Surface electrodes placements are shown in figure 2.

The used device collects real time biosignals at a frequency rate of 5 kHz and EMG sensors have second order band pass filter with *cutoff* frequencies of 25 and 450 Hz . Data is transmitted via bluetooth to a computer, where the signals can be saved and visualized.

2.3 Acquisition Protocol

Subjects were asked to seat and place both hands on a desk, 10 cm away from each other in a parallel position and with hand palms facing each other in 90 degrees of flexion with the elbow. Subjects had to elevate both index fingers vertically with a maximum articular amplitude in a direction opposite to the other fingers position, hold that position for 3 seconds while maintaining a certain force/pressure and then return to the initial position, where it remains for 3 seconds while relaxing as much as possible. This movement was repeated for 5 minutes or less according to maximum time tolerated by the patients. The coordinated movement was guided by a programmed sound and

both fingers had to be as much coordinated as possible one to another. The protocol was used for both contra and ipsilateral acquisitions.

3 SIGNAL PROCESSING

The acquired signals were processed using Python language. Signals were filtered by a third order Butterworth band pass filter of $30-2000$ Hz. In order to extract information about coherence and PLF, intervals of contraction common to both signals had to be isolated from intervals of relaxation, since coherence is better estimated during periods of steady contraction (Fisher et al., 2012). Signals presenting higher amount of noise will conceal real information, inhibiting to distinguished contractions from relaxation intervals. This and the differences among individual signals, does not allow to predefine an onset value common to all signals. So, instead of using a method based on the EMG signal envelope, a method based on statistical model was used to define contractions onset. Initially, more than one value was assigned to both on and offset for each contraction. In order to obtain the correct on and offset for each contraction, the excessive ones were removed when: (1) the number of samples between the on and offset is too short or (2) when the number of samples between the off and following onset is too short. To guarantee that these signals have common intervals of contractions, it is chosen, for each contraction, the highest value from both onsets and the lowest from both offsets.

3.1 Coherence Processing

A first analysis was performed using a long interval of contraction record. The signal was divided on two equal epochs, and the coherence between them was computed. Regarding the EMG signals, they were full-wave rectified before any fast Fourier transform (FFT) analysis. Sampling frequency is placed as 5 kHz, the nonequispaced parameter of the FFT (NFFT) as 2048, and the value that dictates the dependency between FFT windows as 1024. Defining all this parameters enables to compute coherence.

Coherence is reported in two different ways. First, to provide a visual representation of coherence dependency on frequency (in the imaginary domain), coherence mean values among intervals of contraction for a given muscle pair was performed across all patients within a group of subjects. This allows to obtain precise coherence values for each patient acquisition based on averaging multiple independent instants of data. Second, to provide an estimation of

coherence dependency on frequency across the population of each group, mean coherence was calculated for the same values of frequency for a given muscle pair among all subjects within the same group. To assure that the wanted band of frequency was present in both signals of each patient, frequency spectra were computed for all instants of contraction and then averaged to present an individual spectrum for each patient.

3.2 Phase Locking Factor Processing

Since the beta-band frequencies seem to be the most relevant for this study, PLF was calculated for specific values of frequency f within this same band $[15, 30]$ Hz with a resolution of 1 Hz. This procedure was performed among both control and patient groups. Each signal was band pass filtered $[f-2, f+2]$ Hz, being f the analysed frequency. Instants of contraction where again isolated and for each, PLF between each pair of contra and ipsilateral measurements was calculated. To present a final value for each member of each group, PLF was averaged between all contractions within the same acquisition. This procedure, is performed as many times as the number of the analysed frequencies. PLF was averaged among all members within the same group to present a PLF value, dependent on frequency choice, for a population.

4 VALIDATION

4.1 Synthetic Electromyography

For validation of the algorithms, synthetic EMG signals were used to compute coherence. To prove that coherence exists between two signals linearly dependent on each other for particular values of frequency, sets of signals were constructed and defined by the following equation:

$$signal = (sin(t \times 2\pi f) + k) \times n(t) \times mod(t) \quad (3)$$

where t is a sequence of integer numbers, incremented by one unit, with a desirable length; t is referred in seconds by dividing the desirable length for 5000, to take into account the sampling frequency. $n(t)$ represents Gaussian noise ($\mu = 0$ and $\sigma = 1$), k is the signal envelope, f is the signal's frequency and the portion $mod(t)$ represents the rest of the division of t by 6 bigger then 3 - guaranteeing instants of simulated contraction and relaxation of 3000 ms.

Multiple signals were created, choosing t : 8, 80 or 391s and f : 10, 20 or 40 Hz. Number of samples were chosen to provide signals with 1, 13 and 65

instants of contractions to decide the more appropriate time sampling for acquisitions. Frequency values were chosen taken into account that beta-band is being studied.

For all created signals, coherence was calculated between two of the same type signals (simulating both right and left hand). Coherence defined by equation 3 is performed for instants of contraction and then averaged for the entire measurement. Coherence results do not present any dependency on the choice of f value, since it assumes one for that same frequency and nearly 0 for the remaining.

On the contrary, coherence results seem to depend on the choice of signals length. Two types of signals were performed, both defined by equation 3, with common value of 40 Hz for f but with different value of t. First, signals with 65 instants of contraction, and second signals with 1 instant of contraction; two sets of signals, with different portions of $n(t)$, were created to test coherence between them. Results of mean coherence for these pair of signals allow to affirm that the higher the signals length, the more accurate are the coherence results. Since noise is randomly distributed, averaging coherence of greater amount of instants of contraction, tends to reduce the SNR. Therefore, the use of long acquisitions increases the precision of coherence.

5 RESULTS AND DISCUSSION

5.1 Coherence Analysis

5.1.1 Ipsilateral

For both simultaneously acquired signals, ipsilateral coherence was analysed for instants of contraction using NFFT as 4096. Graphical representation, for a patient and a control subject, is shown in figure 3. Analysing results, it is possible to observe that the signal acquired from the patient presents coherence near 0 for all frequencies, while coherence from the control subject presents higher values for most presented frequencies, despite the fact that beta-band is not distinguished from the remaining frequencies.

Differences are significant since for beta-band, coherence mean value for the patient was 0.024 ± 0.013 and for the control subject 0.694 ± 0.040. Patient results would be expected since coherence in beta-band is not visible for ALS. On the other hand, results from the control group are not expected since coherence values were higher than those observed in literature. Differences in results may be explained by differences in acquisition protocol, used algorithm or parameters.
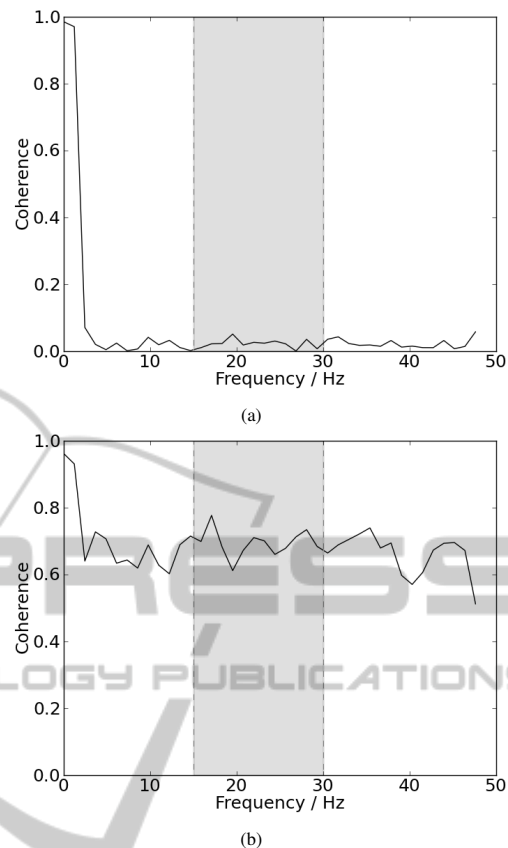

Figure 3: (a) Ipsilateral coherence acquired from a patient. (b) Ipsilateral coherence acquired from a control subject. Delimited by the grey box, are represented the frequencies corresponding to beta-band.

5.1.2 Contralateral

Prior to coherence analysis, the presence of beta-band frequencies was tested, recurring to frequency spectra analysis. Instants of muscular contraction were isolated and full-wave rectified. The power spectrum was calculated and averaged within all contractions; these frequency spectra were performed by PSD calculus. Graphical representations of these results for patients group are shown in figure 4(a), and for control group in figure 4(b), both with NFFT as 2048.

In figure 4, results show a higher presence of beta-band frequencies, since they appear more enhanced than the remaining, for the majority of all results from both hands and groups. When the frequency spectra reveal the presence of beta frequencies, one can evaluate the values of coherence within these band frequencies. As shown in 5.1, ipsilateral coherence appears to be a precise indicator of neuronal degeneration development. Contralateral coherence is tested to check whether results are similar to those obtained for ipsilateral acquisitions. Contralateral coherence between
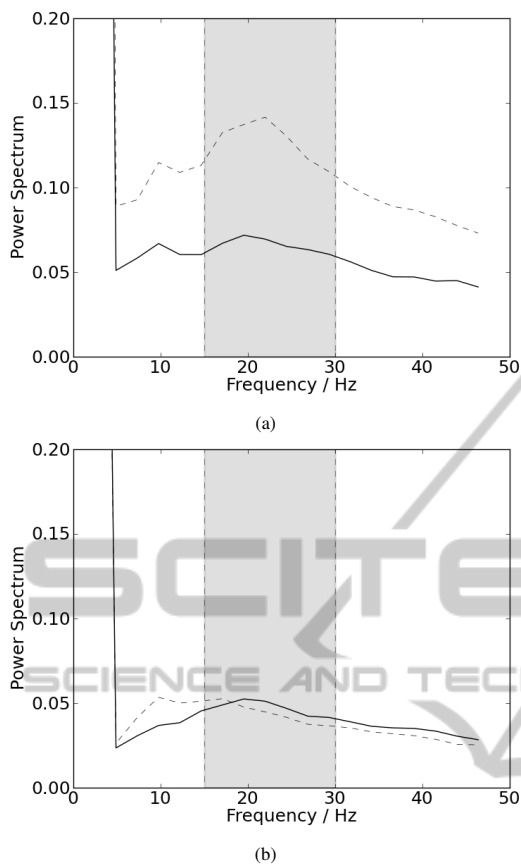
(a)

(b)

Figure 4: Representation of the power spectra. Results collected from the left hand are represent by the dotted line and results collected from the right hand are represent by the straight line; delimited by the grey box, are represented the frequencies corresponding to beta band. (a) Results for the group of control and (b) for the group of patients.

both interosseous muscles, one from each side, are shown for patients and control subjects groups in figures 5(a) and 5(b), respectively.

Results from the control group are not entirely similar to those observed in literature. Coherence values for the beta-band frequencies do not stand out from the ones presented in the remaining frequencies. There was no significant intermuscular coherence present on any of the two groups for beta-band. Pooled coherence value for the patients group was 0.0069 ± 0.0019 and for the control group 0.0031 ± 0.0017. Coherence was present within significance (in the same order of magnitude found in literature), but not higher on the beta-band than the remaining other frequencies. The analysis from the group of patients shows a behaviour similar with the group of patients. Contralateral coherence between coactivated muscles from left and right side is not considered significant within the beta-band. Therefore, despite the possible presence of these frequencies (beta-band) on
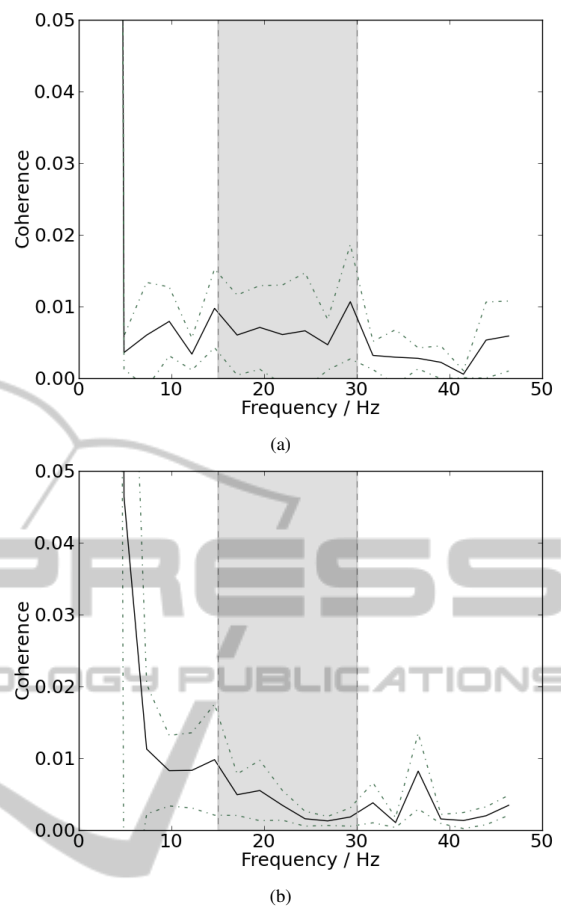

(a)

(b)

Figure 5: (a) Contralateral coherence acquired from a patient. (b) Contralateral coherence acquired from a control subject. Delimited by the grey box, are represented the frequencies corresponding to beta-band.

both signals, they do not significantly depend linearly from each other.

5.2 PLF Analysis

5.2.1 Ipsilateral

To present a final value for each member of each group, PLF was averaged between all contractions within the same acquisition, for each value of frequency among beta-band. Therefore, this procedure is performed as many times as the number of studied frequencies. PLF was averaged among all members within the same group to present pooled results, for ipsilateral measurements. The frequencies of interest and its respective PLF values are represented in figure 6.

The results in figure 6(a) are similar to those obtained in 5.1.2. PLF values do not stand out from the remaining in beta-band and do not assume significant
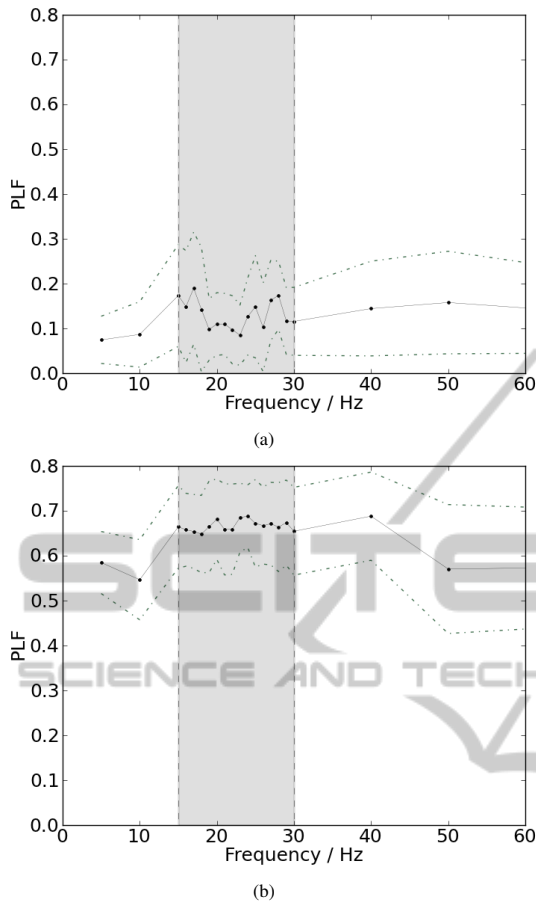
Figure 6: Schematic representation of mean PLF values as a function of frequency, for ipsilateral acquisitions, depicted as a straight line; standard deviation is displayed as a dotted line. Delimited by the grey box are represented the frequencies corresponding to beta-band. (a) Results from the group of patients. (b) Results from the control group.
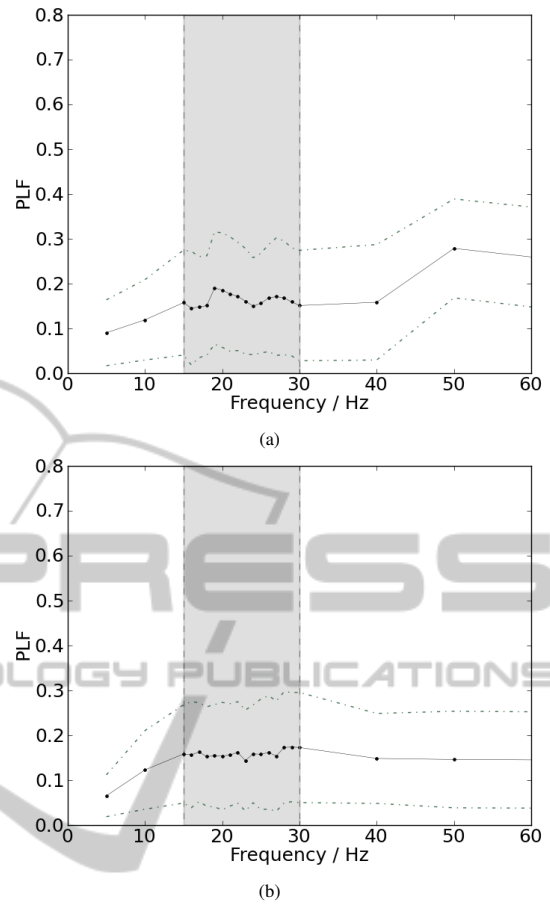

Figure 7: Schematic representation of mean PLF values as a function of frequency, for contralateral acquisitions, depicted as a straight line; standard deviation is displayed as a dotted line. Delimited by the grey box are represented the frequencies corresponding to beta-band. (a) Results from the group of patients. (b) Results from the control group.

values for any frequency. On the other hand, observing figure 6(b), PLF assumes much higher values and beta-band frequencies appears to stand out from the remaining. Differences are significant since for beta-band, PLF mean value for the patient was 0.131 ± 0.031 and for the control subject 0.6664 ± 0.0093.

5.2.2 Contralateral

Mean PLF values for the beta band in contralateral signals, as a function of frequency, are presented in figure 7, for the group of patients and group of control in 7(a) and 7(b), respectively. As observed in both graphical representations of figure 7, PLF values do not significantly stand out for the beta-band frequencies, since for beta-band, PLF pooled value for the patients group was 0.1169 ± 0.0068 and for the control subject 0.1169 ± 0.0057.

6 CONCLUSIONS

Synthetic EMG signals with a specific known value of frequency were used to test coherence between two signals of the same type, to find whether coherence among them is present for that frequency. For two simulated signals of instants of contraction and relaxation with the same frequency, mean coherence between them for instants of contraction, are close to 1 for the specific frequency and near 0 for the remaining. Varying signals frequency value does not change coherence general trends. Altering these signals length, changes the number of instants of contraction used to present final averaged coherence, and the lower the number of samples, the higher will be the influence of noise.

Both coherence and PLF analysis in ipsilateral

acquisitions present significant differences between both groups of patients, as already proved by previous publications (Fisher et al., 2012). Results from the group of patients present no significant differences from the results obtained for contra lateral acquisitions while the group of subjects, presents higher values of PLF and coherence for all frequencies, especially for beta-band. So, it is possible to assume that while control subjects present no neuronal or muscular anomalies and therefore higher synchrony for beta-band, patients with ALS do not present synchrony in any frequency, specially for beta-band. All results allow to conclude that ipsilateral analysis is a good measure of corticospinal pathways integrity. Frequency spectrums were performed for contra lateral acquisitions and it was demonstrated that beta-band frequencies are present in instants of steady contraction. But, as proved by coherence and PLF analysis beta-band frequencies in contralateral acquisitions was not present in neither for patients or control subjects. Neither differences or significance values were found for both control and patients. Therefore, it is to conclude that contra lateral frequency analysis is not a good marker for beta-band frequencies studies. Comparing both methods used to study frequency domain, PLF analysis may be seen as a more practical method since it requires smaller sections of data, compared to coherence. On the other hand, PLF can only be analysed for a specific value of frequency, while coherence is analyzed for the range of frequencies presented on data. To conclude, as further work is suggested to rely on the possibility of using PLF analysis to observe beta-band and assess about neuronal pathways integrity in ipsilateral acquisitions. Therefore, it seems possible that studying PLF serves as a method of diagnosing ALS.

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