EVIDENCE FOR THE CENTRAL OSCILLATORS IN THE PHYSIOLOGICAL TREMOR GENERATION PROCESS

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Physiological tremor is a complex signal resulting from interactions between several mechanical and neural factors. In this paper we bring into discussion only the neurogenic components that, first, have been mainly attributed to spinal interneuronal systems or subcortical oscillators but more recently, also to cortical rhythms. Here we investigated, using visual stimuli at different frequencies (5Hz, 10Hz, 15Hz), whether the major contribution of the central oscillators in the physiological tremor is supported by the analysis of physiological hand tremor. To detect a rhythmic central drive to the muscles, which is independent of peripheral mechanics but dependent, by indirect pathways, on the stimuli frequency, we used second order spectra (auto- and cross-spectral analysis) and, also, the coherence analysis of the tremor signals obtained with and, respectively, without stimuli. Additionally, we modeled the tremor's underlying linear process by an autoregressive (AR) process of order 4. The AR model's parameters were, then, used as inputs for 2 classifiers, implemented with 2 neural networks (NNs). The obtained results confirm the hypothesis.

1. Introduction

Physiological tremor (PT), as also other types of tremor (enhanced physiological tremor, essential tremor, Parkinsonian tremor etc.), was subject to numerous studies aimed to find its real mechanisms and origins. But, even so, we still know little about these. Physiological tremor – defined as the involuntary, oscillatory movement of parts of the body, mainly the upper limbs [1] – is a complex signal resulting from interactions between several mechanical and neural factors [2]. It is considered to be a realization of a linear stochastic process and its spectrum contains the corresponding two types of components - a mechanical reflex component of tremor (due to the natural resonant frequency of the limb segment) and, respectively, the neurogenic components -, their identification being possible by increased inertial loading [2].

Neurogenic components have been shown to contribute to two distinct frequency bands of the tremor spectrum, namely 8-12 Hz and 15-30Hz [3].

For the first frequency band, the recent finding of highly correlated muscle activation between the left and right side of the body in cases with abnormal bilateral corticospinal connections in congenital mirror movements [5] led to the hypothesis that the cortex might be involved in this component generation of the tremor signal. The phase spectra delay between cortex and muscle, compatible with conduction in fast pyramidal pathways, reported recently in the literature [6], also indicates a cortico-muscular transmission of the oscillation rather than peripheral feedback to the cortex. Regarding the higher frequency range oscillations there are some results which claim their origins correspondence with the EEG activity in the beta and gamma bands [7]. But, despite all evidences reported in the literature for how could these tremor components arise, a clear demonstration of tremor at these frequencies is clearly lacking from most standard physiological tremor studies.

In this paper we propose a new methodology to assess the existence of a central driving oscillation confined in the physiological postural tremor signal. For this we used the so called *photic driving* that is routinely used as an activation method in clinical EEG recordings; it conduct to EEG responses that show the same frequency as the flickering stimulus – namely SSVEPs (steady-state visual evoked potentials) [8]. In the proposed method we consider the brain to be a black-box (in which the large reciprocal interactions between diferent brain areas control the way that oscillations propagate) and test for any new and specific characteristics induced by the new cortical state in the tremor signal neurogenic components. Moreover, this approch allows for a conclusion regarding a possible interaction between the visual modality and the central oscillator responsible for part of the tremor neurogenic components.

2. Materials and methods

In this study we investigated, using visual stimuli at different frequencies (5Hz, 10Hz, 15Hz), the influences between the visual stimulus and the variability of the tremor signal parameters.

Two subjects were admitted. The both subjects were right-handed. They were healthy, with no known neurological or endocrine pathology, and no known Ca2+ or Mg2+ deficiency. In addition, they have taken no medication during the week previous to the recordings. All subjects have been explained all procedures and gave written consent regarding the participation in the study. The entire procedure of tremor acquisition was unobtrusive for the subjects, with no physical contact, due to the sensor capability.

The recordings sessions were scheduled several days until the acquiring of the entire data set was finished (88 recordings: subject 1 – 20/5Hz, 18/10Hz, 10/15Hz; subject 2 - 20/5Hz, 10/10Hz, 10/15Hz). Each recording had 98.4 s, but only the first 32.8 s and the last 32.8 s, of hand tremor, were kept. After the first time segment of 32.8s a visual stimuli, at one of the specified frequencies, was presented to the subject. In all this time the seating subjects were asked to maintain the hand in the same postural position. The initial position was with the hand placed parallel with the transducer [11] and the center of the palm pointing exactly the center of the transducer. More, the subject elbow was fixed by a mechanical support in order to preserve the tremor characteristic unaffected by the hand fatigue influence in the last part of the recordings. In order to isolate them from all kind of surroundings stray stimuli, all the recordings took place in a quiet room without any source of light. Also, the subjects were asked to think at nothing. All the time the subjects looked to a computer display. In the first part of the recording the display was a uniform black background. After the 32.8 s the stimuli was presented. The stimuli consisted in a circle, of 2 cm radius, placed in the middle of the display changing his luminosity between a black background followed by a white flash. The stimuli changes pattern is a symmetric rectangular wave with the desired selectable frequency (5Hz, 10Hz, 15Hz). The subjects had no visual control of their hand position. The sampling rate was 250 samples per second and we got 8.200 samples per each acquired segments of the recording.

Each time series (of length P) has been normalized to unity variance and zero mean value and, then, it has been divided into disjoint (non-overlapping) sections of 4,096s duration; thus we obtained L complet disjoint sections, each of length T (P=8200, T=1024, L=8) for each time series. Time series data from each disjoint section were Fourier-transformed, giving a frequency resolution of 0.004 Hz. No tapering or weighting function was used. The finite Fourier transform of the l^{th} segment ($l=1...L$) from each time series $S(t)$ (signal with stimuli) or $N(t)$ (signal without stimuli) at frequency λ is denoted by $F_x^T(\lambda,l)$ and defined as:

$$F_x^T(\lambda,l)=\int_{(l-1)T}^{lT} x(t)e^{-i\lambda t}x(t)\approx\sum_{t=(l-1)T}^{lT} e^{-i\lambda t}x(t) \quad (1)$$

where: $x(t)$ is replaced by $S(t)$ *–signal with stimuli* and respectively, $N(t)$ – signal without stimuli.

Auto- and cross-spectra were, then, estimated by averaging over the disjoint sections [9]:

$$\hat{f}_{xy}(\lambda)=\frac{1}{2\pi LT}\sum_{l=1}^{L}F_x^T(\lambda,l)\overline{F_y^T(\lambda,l)} \quad (2)$$

where: the overbar '$\overline{}$' on $F_y^T(\lambda,l)$ indicates a complex conjugate and (x,y) are the pairs (S,N), respectively (S_1,S_2) for cross-spectra, and (N,N), respectively (S,S) for autospectra. The pairs (S,N) is given by the two time series of tremor signal with, and, respectively, without stimuli, acquired in a single recording of 98.4 s. The pairs (S_1,S_2) is given by two time series of tremor signal with stimuli, acquiered for the same frequency, in different recordings of 98.4 s. *Coherence estimate* for two signals was computed using the formula:

$$\left|\hat{R}_{xy}(\lambda)\right|^2=\frac{\left|\hat{f}_{xy(\lambda)}\right|^2}{\hat{f}_{xx(\lambda)}\,\hat{f}_{yy(\lambda)}} \quad (3)$$

The sample coherence indicates the degree of linear correlation in the frequency domain between two signals on a scale from zero (independence) to one (complete linear independence). The complex valued function representing the square root of Eq. (3) is called *coherency*. After applying Fisher's transform, Tanh^{-1}, to the magnitude of the estimated coherency, the variance of the new obtained variable is given by the constant value: $\sigma^2=\frac{1}{2L}$, where L is the number of disjoint sections used to estimate the coherence [9].

We calculated then a statistical test to assess that the individual coherence estimates for all the pairs (S,N) (respectively, (S_1,S_2)) have a common mean. For each k pairs (S,N), we have for analysis only k/2 pairs of (S_1,S_2). For the k coherency estimates, m_i, we can estimate the common mean as:

$$\overline{m}=\sum_{i=1}^{k}\frac{m_i}{k} \quad (4)$$

and design the statistics,

$$\sum_{i=1}^{k}\frac{(m_i-\overline{m})^2}{\sigma^2} \quad (5)$$

which, under the null hypothesis, is distributed approximately as χ^2 with (k-1) degrees of freedom. The computation of Eq. (5) was done separately at each frequency, λ, over de range [0,125] Hz. A confidence limit at the 95% level was set at the value $\chi^2_{(\alpha;k-1)}$ and the null hypothesis was rejected if the Eq. (5) exceeded this limit.

To facilitate the interpretation we calculated the *pooled coherence estimate* given by Eq. (6), which has values constrained also within the range 0 to 1. The upper 95% confidence limit for the estimate of Eq. (6) besed on the assumption of independence between the k pairs of processes is given by Eq. (7)[10].

$$\frac{\left|\sum_{i=1}^{k}\hat{f}_{xy(\lambda)}\,L\right|^2}{\left(\sum_{i=1}^{k}\hat{f}_{xx(\lambda)}\,L\right)\left(\sum_{i=1}^{k}\hat{f}_{yy(\lambda)}\,L\right)} \quad (6)$$

Values of the pooled estimate of coherence lying below this line can be taken as evidence that, an average, no coupling occurs between the two processe

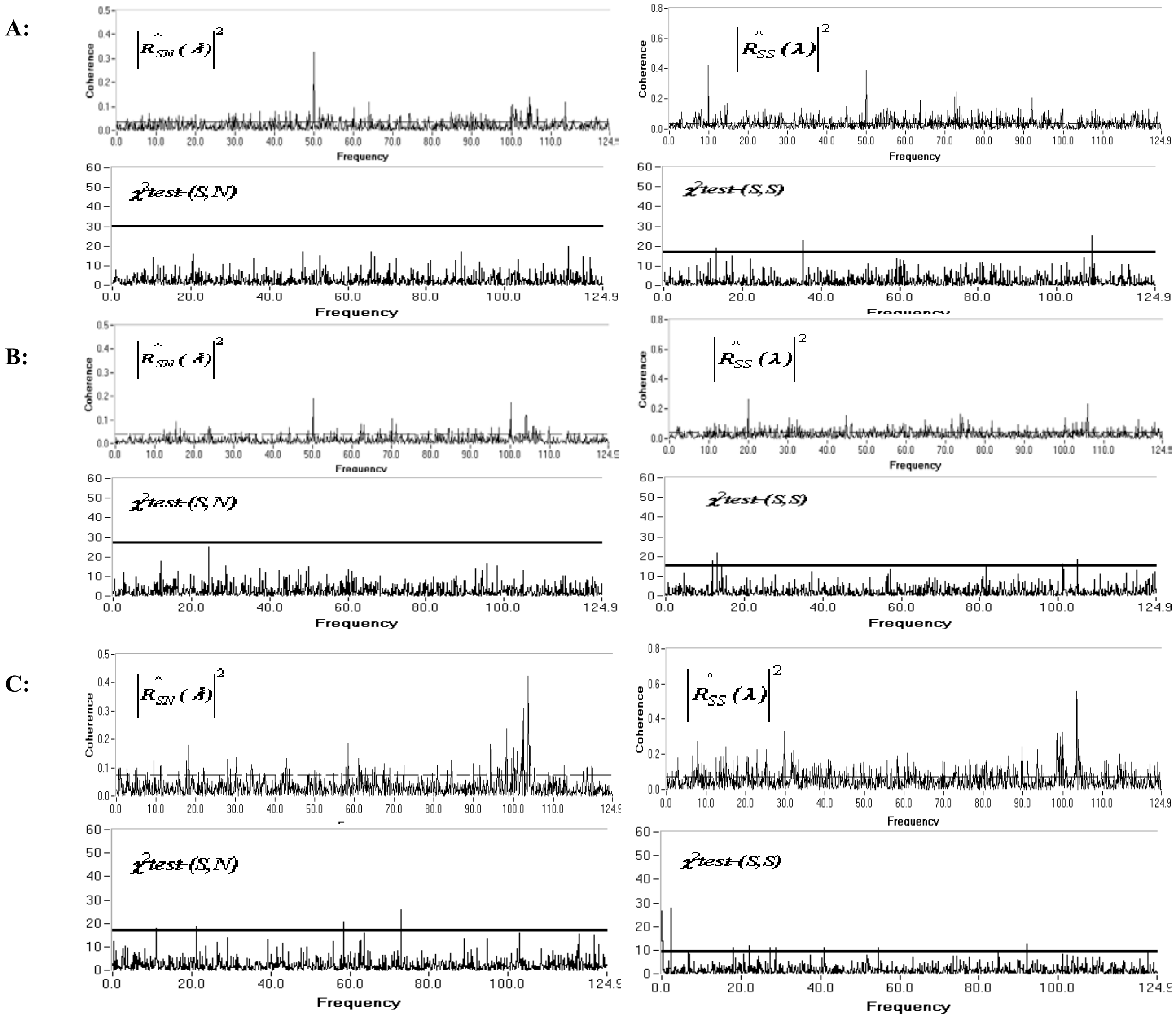

Figure 1: Pooled coherence and the coresponding χ2 test for signal (with stimuli-without stimuli) – left column and (with stimuli-with stimuli) – right column, for 5Hz, 10Hz and 15Hz frequency stimuli (A,B,C).

(*x,y*) at a particular frequency λ. We can also interpret Eq. (6) as representative of each coherence estimate between the *k* processe only if the null hypothesis that the *k* transformed coherency estimates have a common mean is accepted.

$$1-(0.05)^{1/(\sum_{1}^{k} L-1)} \qquad (7)$$

Additionally, two neural networks (NNs)– with a multilayer perceptron structure – were used, further to validate or maybe invalidate the results obtained from the spectral and coherence analysis. The first NNs inputs were the coefficients of an autoregressive (AR) process of 4th order used to model the tremor's underlying characteristics, associated to all stimuli frequency. The estimation of the AR model's parameters for all the tremor signals, on sliding windows of 252 samples, half overlapping, were made by using the Yule-Walker method. At the first NN outputs corresponded the three natural classes (5Hz, 10Hz, 15Hz). The second neural network had as inputs the AR model's parameters estimated for all the tremor signals acquired with and without stimuli and it had as outputs the corresponding four classes (none, 5Hz, 10Hz, 15Hz). The output layer had as activation function the SoftMax that gives a probabilistic interpretation of the output. We used 1536 samples for the first NN's training set (T) and 384 samples for the cross-validation set (CV). For de second NN we had T=2048 and CV = 512. In order two achieve the best classification rates several topologies were tested.

3. Results

The results obtained with this new methodology are partially illustrated in Figure1. One can see here the coherences and its upper 95% confidence limits depicted only for one of the subjects and for all frequency stimuli. The same outcomes were achieved also for the other subject. The coherence graphics exhibit a clear coherence at 10Hz (for the 5Hz frequency stimuli) and 20Hz (for the 10Hz frequency stimuli) and, also, at 50Hz and 100 Hz (hum noise) for the pairs (S,S). Also for the 15Hz frequency one can see a peak at 30Hz that seems to relieve but it is not so evident as the others two. The χ^2 test certify the representativeness of the pooled coherence estimate for all k individual coherence estimates and for almost all λ frequencies.

The other results, designed to validate or not the first results, were attained using a multilayer perceptron with two hidden layers. The first hidden layer was formed by 6 PEs and the second by 4 PEs. Based on this topology the maximum performances were obtained. The preliminary classification rates were as following in table1 thus validating the first results obtained with second order spectra estimates.

Table 1: Correct classification rates (%)

	5Hz	10Hz	15Hz	None
NN 1	**80.33**±3.48	**60.78**±6.52	**16.93**±4.67	-
NN 2	**75.36**±1.53	**66.37**±3.42	**19.84**±7.05	**9.83**±4.44

4. Discussion

The evidence of clear distinct tremor characteristics exhibited by the tremor without vs. tremor with stimuli confirm the central major influence in hand PT generation. This evidence also claim for a relationship that is manifestly established between the visual cortical projections and the central oscillator driving the PT. How this happens it is still unclear but some hypothesis could be advanced: 1) the reactive alpha rhythm (8-12Hz) seems to originate in the medial parieto- occipital sulcus (a visual-motor coordination area that it is one of the pathways through which visual information reaches parietal cortices, the *site of central oscillator*); 2) the steady-state potentials exhibits clear resonance phenomena around 10, 20, 40 and 80 Hz [12] and this could be a potential neural basis for gamma oscillations in binding experiments; 3) experimental data indicates that gamma rhythms are used for relatively local computations whereas beta rhythms are used for higher level interactions involving more distant structures and longer conduction delays, corresponding to signals travelling a significant distance in the brain.

Another aspect which seems to be partially contradictory with our expectations is that of the significant coherence values which occur at double the frequency stimuli. Indeed, this could not be a problem if the visual sensorial field interpret each succesive colour presentation (white/black/white etc.) as a distinct stimulation, thus coding the information at double the designed frequency stimuli.

5. Conclusions

This paper has attempted to illustrate central origins of the PT and also highlighted the potential of studying rhythmic CNS activity through investigation of physiological tremor.

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