TREMOR MEASUREMENTS FOR CLARIFYING THE HYPOTHALAMIC PROCESSES AND GABA CONTROL

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Abstract: We thoroughly investigate the tremor signal general behavior and the effect of visual stimuli on tremor. The research sheds light on the intimate processes producing tremor, on the tremor physiology and on the methodology to measure tremor for diagnosis purposes.

Introduction

The study was designed to test two related hypotheses regarding the tremor. *First*, we address the hypothesis of the existence of neuronal pathways and of the influence between the cortex visual area and the brain centers involved in the control of involuntary hand tremor movements. *The second* question is what role gamma-amino butyric acid (GABA) plays in the relationship between the upper and the lower central nervous system (CNS).

One of the major characteristics of the Parkinson's disease generated the idea of this study. It is known that uncontrollable tremor of the extremities disappears during voluntary movements and starts to increase in amplitude in the case of intellectual effort [1]. These symptoms suggest the existence of an influence between the brain centers involved in these two processes. But, in other kinds of pathological tremor, such type of relation does not exist.

It is known that in several diseases, tremor significantly changes, due to mechanisms originating in different parts of the CNS [6]. Moreover, it is known that tremor itself originates in several parts of the CNS [2]. For instance, there is a type of tremor due to lack of suppression of excitation to movements in the cerebellum, while there is another type of tremor, apparently originating in the upper CNS, due to emotions. Therefore, we ask the following question: *can it be proved, by measurements on tremor – not by inferring from the neuronal connections in the CNS – that tremor originates in a complex loop in the CNS?* Related, we put another question: *is there any "tremor reflex" that could substantiate the answer to the previous question?* For example, *is there a visual reflex in tremor, changing the tremor parameters?*

Normal tremor is not well understood. It is not known if normal tremor reflects some necessary process, like fatigue adaptation mechanism, or just a random activity. If purely random, tremor should be stationary under fixed conditions. If not random, it might reflect internal biological processes and states.

To answer the question on the randomness of the tremor processes that are more intricate must be addressed. It is believed that GABA is the essential regulator in controlling the neuronal firing activity. While "free" (unregulated) neurons may fire in a purely uncorrelated (thus random) way, GABA keeps the firing under control.

Because the release of GABA decreases with age, it is assumed that tremor increases with age and several neurological diseases involving increased tremor are related to GABA insufficiency. However, normal tremor can tell us much about the intimate control of the firing and the related generation and release of GABA. Determining the specificity of the nonstationary process represented by the tremor, we obtain indirect, yet valuable information about the efficiency of the GABA control and on its long-term stability. Studying the influence of upper CNS effects on the tremor, like visual stimuli, we may obtain information on the control of GABA release at lower CNS locations, like hypothalamus, by the cortex.

In our study we used the tremor signal to identify the correlation between the brain centers mentioned above. The tremor signal was acquired with a specially designed sensor embedded in the measurement system.

Experimental setup

The operating principle of the sensor [7] is based on the property that an element generating an external electromagnetic field changes its impedance due to the properties of the objects in its close vicinity. A planar winding composes the sensor, as shown in Figure 1. The winding has a relatively large conductor width and a relatively small spacing between successive turns, in order to achieve a suitably high capacitance between the turns, a suitably large overall capacitance for this resonant sensor and to provide a relatively uniform electro-magnetic field, in the 3D input sensing zone.

The sensor operates in the linear part of the characteristic [7], Figure 1, and, more than that, the bandwidth of the transducer is appropriate for the acquisition of the tremor signal. Basically, this is due to the high frequency operation of the sensors (16 MHz). Based on these transducer characteristics, the tremor signal acquired with the sensor is a very reliable one.

When the hand is above the sensor, the output of the driver circuit has a high value. The distance between the sensor and the hand is the factor that influences the magnitude of the output signal of the driver circuit.

The sensor is driven by an electronic control unit [3], [8], sketched in Figure 1. The "heart" of the electronic unit is the digital signal processor (DSP) TMS320F240 manufactured by Texas Instruments™. It drives the sensors, filters the signals, acquires hand tremor movements and transmits the tremor signal to the PC.

The tremor signal is sent through the standard serial line to a program used to interface with the device, to transfer, to save and to present the tremor signal. The software used to manage the tremor acquisition and to store the data was written in Microsoft™ Visual C++ with the Measurement Studio ComponentWorks++ from the National Instruments™ and it is an improved version of the software presented in [8].

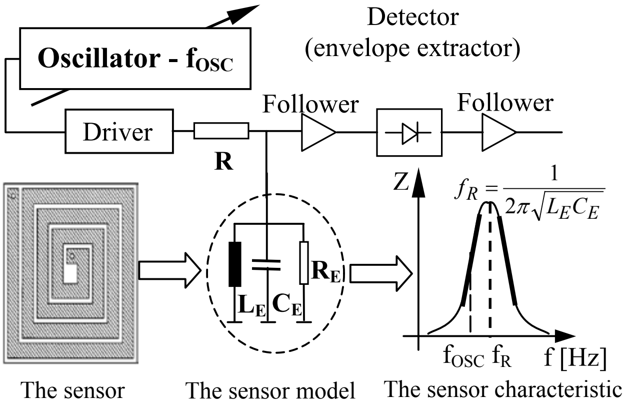

Figure 1: The sensor and the driver circuit

Methodology

We admitted five subjects for this study, three of them males and two females. All subjects were aged between 26 to 29 years. All subjects were healthy, with no known neurological or endocrine pathology, and no known Ca^{2+} or Mg^{2+} 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.

In order to visually isolate them from the surroundings, the subjects have been placed to look to a computer display, keeping their head placed in an enclosure with four non-transparent walls. Also, they were asked to think at nothing specific. In one series of tests, the display was blank, while in another series of tests, a single change of the visual stimulus, at the middle of the session, was produced.

For every subject we had two sessions, each of them scheduled on a different day, with each session containing ten recordings. One session was performed using the visual stimulus and the second without using it. In a recording session, the subjects were seating and watching the display that was presenting a stimulus pattern; during the experiment the subjects kept their hands just above the transducer. The display was placed at half meter in front of the subject. Initially, the display presented to the subject a green background, with a red square positioned in the center. The stimulus consisted in reversing the colors in the image (green square on a red background). All the recordings took place in a quiet room, with dim light.

In all recording cycles, the subjects were asked to maintain the hand in the position mentioned above. The initial fixed position was with the hand placed parallel with the transducer and the center of the palm pointing exactly the center of the transducer. All the users fixed the hand at the same vertical distance from the sensor, marked by a rule maintained in position by a support. During the recording time, the subjects had no direct visual control of the hand, thus preventing any visual feedback.

The signal has been acquired with the sampling rate of 250 samples per second and we obtained 15.000 samples per each recording cycle. In the case of the visual stimulus experiment, the first 7500 samples correspond to the first 30 seconds of recording, that is just before the stimulus was presented; the others 7500 samples correspond to the last 30 seconds of recording.

Preprocessing

The hand has a complex movement. The other components that compose the whole signal (that is, the acquired signal) are derived from the respiratory movements and from other movements, unrelated with the tremor, like heart movements. The respiration contributes to the low frequency spectrum of the hand tremor signal. These components must be removed, knowing that the respiration has a basic frequency around 0.1 up to 0.3 Hz for adult subject, with a band in the range of 0.05 to maximum 3 Hz. After the PC software receives, in a serial mode, the tremor signal, a high-pass filtering at 1 Hz is applied. The resulting signal is smoothed using the moving average method with a window of 10 samples.

An appropriate windowing technique was used to minimize the spectral mixing problem. The Hanning window was chosen, based on its good frequency resolution (the width of the main lobe at –3dB is 1.44 bins) and based on its low spectral leakage (the side lobes roll-off rate is 60 dB/decade). As our data were sampled at 250 samples/s and the FFT was made on 4096 samples, the discrete frequencies were placed at 0.061 Hz intervals.

Visual stimuli evoked in the tremor movements

Subsequently, we address the hypothesis that a visual stimulus may influence the characteristics of the tremor signal. To achieve this goal, we performed time and frequency analysis, using linear and nonlinear methods. The aim of the analysis has been to evidence any change due to the visual stimulation in the tremor time series. For this, we split each time series in four segments. The first segment was formed by the 4096 contingent samples that were taken before the stimulus was presented to the subject. The other three time series split uniformly the recorded segment acquired after the stimulus was presented to the subject.

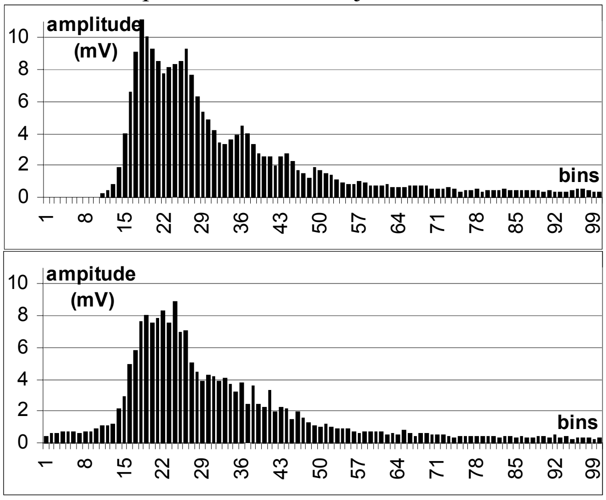

Figure 2: The spectrum frequency (a) before and (b) after the stimulus

First, we have performed an analysis in the time domain. For each subject, a resulting time series was obtained, by averaging all preprocessed time series, after squaring the values of the samples, similarly to the evoked potential (EP) detection method. Unlike the EP case, this method has not revealed a statistically significant change in the tremor in the time series after the visual stimulation.

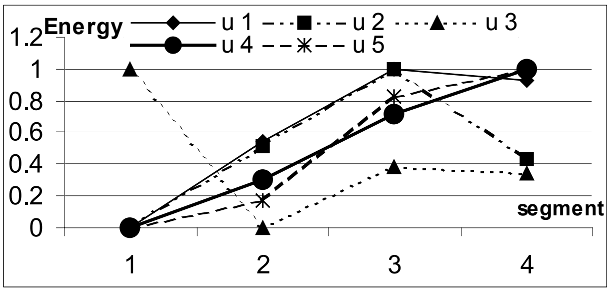

Figure 3: The variations of the sensitive frequency normalized parameters components to the visual stimuli.

In the second analysis, the investigation was done in the frequency domain. On each preprocessed time series, obtained from a subject, the Fourier transform [4] was computed. The resulting spectra were averaged, on each of the four segments, in part. In the Fourier the difference between averaged spectrum, previous and after the stimulus domain can easily be seen, as shown in Figure 2. To compare such frequency distribution, for each segment of the time series, three parameters were computed. The first one was the energy in the bins with number 11 to 25 and the next two were the energy in the bins with number from 25 to 55 and from 65 to 100, respectively. The obtained parameter values showed that the energy in the bins interval 11 … 25 is the most sensitive one to the stimulus, while the energy contained in the bins interval 25 to 55 is less sensitive.

The results are presented in Figure 3 and 4. In these figures, we present the evolution of the energy contained in the intervals 0.671 Hz … 1.525 Hz (bins interval 11…25), for all the five users (u1…u5 represent the users) and corresponding to each of the four segments. The Figure 3 presents the case when the stimulus was presented and the Figure 4 shows the results obtained without the visual stimulus. In Figure 4 we remark that the power-type features fill almost the entire features space; it make us to conclude that in the process there was no type of synchronism. In the meantime, it can be observed, accordingly Figure 3, the existence of some kind of relation or similar behavior of the features extracted for different users when the stimulus was presented. The increasing of the power features on the segment two and three (Figure 3), that are the firsts after the stimulus, reflects an increasing of the amplitude components in the band where the “main frequency” (the frequency corresponding to the highest peak) is presented. Thus, we can conclude that the tremor movement increased.

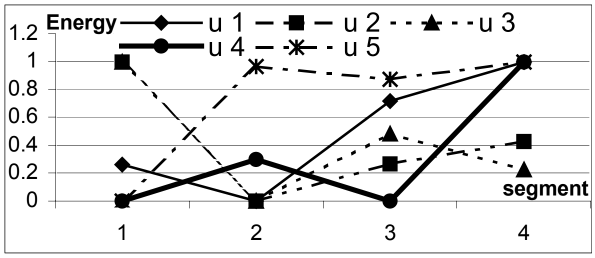

Figure 4: The random variations of normalized frequency-type features with no stimulus

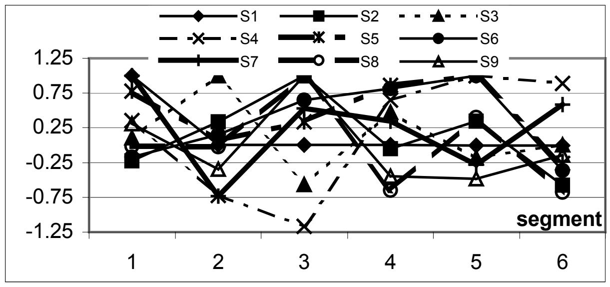

Figure 5: The moments of order 3 for nine time series of a single user. s1… s9 denote the acquired time series from the same subject.

Analysis of the stationary

Due to the poor results obtained in the time domain, as reported in the previous paragraph, a statistical analysis [5] was performed in order to emphasize some common behavior exhibited by the tremor series obtained after the stimulation. This time, the tremor signal with the stimulus is split into five non-overlapping segments of 1500 samples. From the segment acquired before the stimulus we took, for our analysis, only the last 1500 samples. For each segment and for all time series, the standard deviation, the statistical moments of order three and four, the skewness and the kurtosis have been computed.

The statistical analysis was proved inefficient for our problem, but it strongly evidences the nonstationarity of the tremor signal. The tremor is not a strictly stationary process; it is not a wide-sense stationary process either.

In Figure 5, the variation of the third moment on nine time series belonging to the same user, on different time segments (the first segment is just before the stimulus, while the others cover completely the rest of the time series) are shown**.** Similar results have been observed on the other statistical parameters.

We have extended the analysis in the nonlinear domain. Two methods from nonlinear dynamics were applied to the tremors segments. Namely, the correlation dimension and Lyapunov quantities were computed on each time segment of the tremor signal. The nonlinear investigation provided inconclusive results for the analysis, see Figure 6, and highlights once again the nonstationary characteristics of the tremor signal.

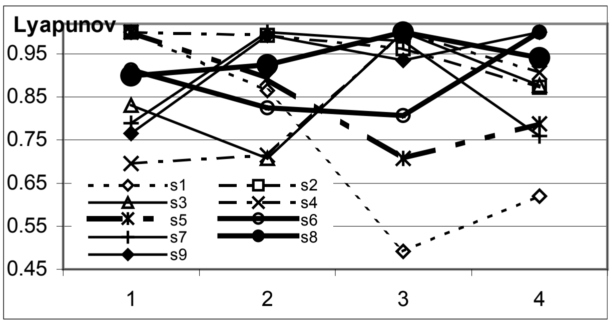

Figure 6: The variation of the normalized Lyapunov exponents in all four segments

Discussions

The changes in the frequency characteristics of the tremor signal due to visual stimuli demonstrate a significant connection between visual regions in the CNS and the thalamic regions basically governing tremor. The lack of evidence that the statistical characteristics of the tremor signal change due to the same visual-induced tremor reflex may indicate that the GABA release in the hypothalamus is modulated by upper regions in a manner involving some periodical process (which is changed, as seen in the frequency domain), but no changes of the basic firing statistics is produced. Moreover, the highly nonstationarity of the neuronal firing process revealed by the nonstationarity of the global tremor shows that the thalamic process may either include a significant randomness, or some process not yet known.

Conclusions

We have investigated the time dependence of tremor signals and the effect of visual stimuli on tremor with the aim of determining relationships between basic motor activity and external stimuli. Moreover, we have paid special attention to the changes in the tremor, which reflects control of the GABA release over time, in view to indirectly determine the fluctuations in this type of intimate neurological control. On longer time periods, tremor, therefore GABA control, is rather unstable. Instability is reflected by the nonstationarity of the tremor and it is subject dependent and it is influenced even by mild visual stimuli, like the one we used. The findings also shed light on the methodology used to measure tremor for diagnosis purposes.

The present research has been aimed to test a few hypotheses, but the testing is yet incomplete. Further research should focus on the functional imaging, to test the conjoint activation of several regions in the CNS, during the change of tremor due to external stimuli. Also, the randomness of the process of GABA control should be addressed in more detailed experiments.

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