Quantification and modulation of tremor in rapid upper limb movements

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Abstract— **Tremor is a manifestation of a variety of human neurodegenerative diseases, notably Parkinson's disease (PD), a chronic disease that affects one in 100 people over age 60 years. Recent research indicates that more than five million worldwide have PD. This disease is primarily caused by a progressive loss of dopamine neurons in the nigrostriatal system that leads to widespread motor symptoms such as bradykinesia, rigidity, tremor and postural instability. Although the diagnosis of PD remains clinical, advances in functional and structural imaging have improved the ability to differentiate between PD and Essential Tremor (ET), as well as between different akinetic-rigid syndromes. No definitive test or biomarker is available for PD, so the rate of misdiagnosis is relatively high. It is therefore crucial to be able to characterize tremor in PD and ET as it is a very common feature at the onset of both diseases. This is made possible with a combination of a neuroscientific and methodological multi-modal imaging approaches, namely kinetic recording methods using accelerometers to quantify tremor amplitude and frequency and functional magnetic resonance imaging (fMRI). These allow the identification of the neural underpinnings of tremor in both PD and ET patients, which in fact have been surprisingly difficult to decipher. In this work we aim to find which tasks involving upper limb movements are suitable to modulate both PD and ET tremor. The same tasks are considered with and without added loading. The resulting analysis will allow designing an efficient fMRI protocol aiming at the identification of the cortical circuits responsible for the modulation of tremor.**

Keywords— **Parkinson disease, essential tremor, tremor quantification, tremor modulation, electrophysiology.**

I. INTRODUCTION

Tremor is an involuntary, oscillatory movement, present in various neurodegenerative diseases. It is caused by the degeneration of the dopaminergic neural system, i.e., the progressive loss of dopamine-producing neurons in the substantia nigra. There are several types of tremor, characterized by different amplitudes and frequencies and that occur in different body parts, with the position of the limbs also playing a role. These different types of tremors are often difficult to distinguish, which would be useful for the differential diagnosis of the underlying diseases [1, 2, 3]. In this paper we focus on two different types of tremor, associated to Parkinson's disease (PD) and essential tremor (ET), respectively. While PD motor symptoms include rest tremor and also rigidity, bradykinesia and postural unbalance [4], ET is commonly described as an action tremor. Both induce hand tremor most prominently, [5].

The genesis of these both types of tremor has not been identified yet [3, 6]. Neuroimaging can play an important role in finding the cortical circuits associated with tremor. This article assesses the impact of different tasks in tremor modulation, providing the framework for setting up an efficient fMRI protocol to study tremor. In order to achieve this goal we define four tasks that comprise different movement combinations and loading conditions. These tasks were performed by three groups: two cohorts of patients (PD and ET) and a healthy control group. The tremor was quantified for each patient and for each task using accelerometers [7]. An offline Fourier analysis of the acceleration in terms of time was used to determine the amplitude as a function of the frequency and ultimately the area under the curve was computed. The resulting data was assessed resorting to statistical tests.

II. METHODS

A. Subjects

Six patients (aged 68±8.44, 3 males and 3 females) were included in this study, all of which attended the Movement Disorder Consultations at Coimbra University Hospitals. Three of them were diagnosed with PD and the other three with ET. The diagnosis was performed by experienced neurologists who were trained in the differential diagnosis of tremor disorders (Hoehn & Yahr: I-III). All patients revealed an asymmetric tremor, the right side being the dominant upper limb. The medication was maintained by patients before tremor recordings. Seven healthy voluntary controls without neurological abnormalities also participated in this study. All the participants were right-handed by self-report. This study and all procedures were reviewed and approved by the Ethics Commissions of the Faculty of Medicine of the University of Coimbra and were conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

B. Procedures

All the participants were seated in a comfortable chair and performed four movement tasks, all of which shared common features, see Figure 1. In particular, they started with each participant placing his arms on his upper legs for 30 sec (relax position). After that, participants performed an ascending and descending arms movement, with a continuous frequency, during 30 sec (arms motion). For each arm, the ascending movement stopped when a shoulder flexion of 90º with the elbow at full extension and forearm pronation was achieved. This procedure (relax position followed by arms motion) was repeated five times. After this, the task ended with the patient placing his arms again in the relax position for another 30 sec. The total duration of each task was 5 min 30 sec. For each task, a total of eleven segments of data were recorded for each arm of each participant – 6 segments corresponding to the relax position and 5 to the arms motion. The tasks differed in the loading conditions and how the arms motion was performed. The first two tasks (task 1 and 2) were performed without any additional load, unlike the other two tasks (tasks 3 and 4), for which a load of 0.5 Kg was placed in each of the participants' wrists. On the other hand, while in tasks 1 and 3 the arms of each participant moved in parallel, in tasks 2 and 4 the arms moved in opposite directions. Each task was carefully detailed to each participant in order to avoid misunderstandings. All the tasks were performed in the conditions described in [8]. The tremor recordings and offline analysis also followed the procedures described in that article.

C. Data analyses

By performing an off-line analysis, the components of the acceleration were obtained as functions of time. A Fourier analysis was performed in Matlab R2012a to obtain the frequency and amplitude of each segment for all the tasks and for each participant's dominant arm. The absolute value of the acceleration was used for that purpose and a band-pass filter was followed (cut-off frequencies 0-3 Hz). Additionally, the amplitude as a function of frequency was integrated for each task segment, using a trapezoidal integration [9], and normalized to the corresponding duration. A total of 11 scalar values were then obtained for each participant and each task. These values are denoted by b_i and m_j (i ranging from 1 to 6 and j from 1 to 5), corresponding to the baseline (relax) and motion segments, respectively. For each participant, the averaged values b and m of the baseline values b_i and the motion segment values m_j were also determined. Finally, for each of the three groups (the two cohorts of patients, PD and ET, and the group of healthy volunteers, the control C), the corresponding values were averaged. A subscript with the name of the group was used to indicate a group average. For example, $m_j^{(C)}$ is the average over all control subjects of the motion segment values m_j.

To visualise the differences between the time evolution profile of the tremor in the three groups, radar charts were obtained for each task, with a clockwise representation of the values of $|m_j^{(G)}-b^{(G)}|$, where G=PD, ET or C. Additionally, Kruskal-Wallis tests were performed for each task to assess for statistically significant differences between groups for the absolute value of m-b. When statistical significance was found, Mann-Whitney U test were performed to compare pairs of groups. All statistical analyses were performed using IBM SPSS Statistics 19.0 software package assuming a 0.05 level of significance.

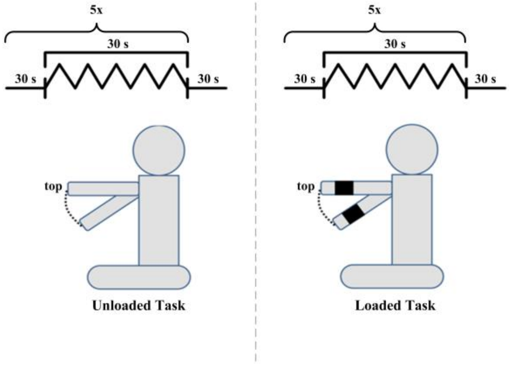

Fig. 1: Schematic diagrams of tasks 1 and 2 (unloaded) and tasks 3 and 4 (loaded). A detailed description of each task can be read in the text.

III. RESULTS

The values of $|m_j^{(G)}-b^{(G)}|$ are represented clockwise in Figure 2 for the unloaded tasks (1 and 2) and in Figure 3 for tasks involving added loading (3 and 4). In the latter the values corresponding to each group maintain the same ranking for all values of j, which is not true for the unloaded tasks. A clear distinction in the profiles of the groups is therefore only visible for the loaded tasks, on which the focus of the remaining analysis is placed.

To assess whether significant statistical differences were detectable between the three groups (PD, ET and control) in tasks 3 and 4, the data was first reduced by averaging the motion segment values m_j for each participant. A boxplot of the values of |m-b| obtained for the volunteers is displayed in Figure 4.

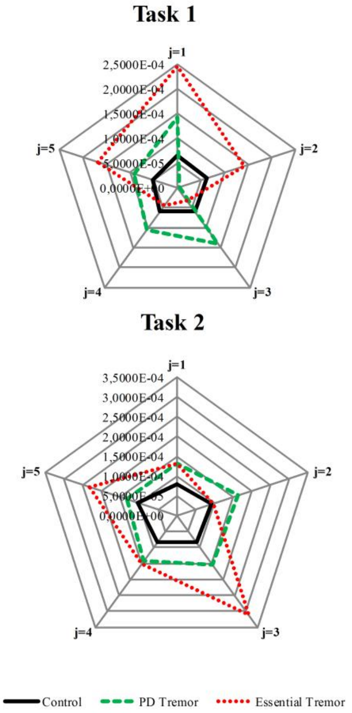

Fig. 2: Clockwise representation of the time evolution of changes in tremor for each group for the unloaded tasks (task 1 and 2).

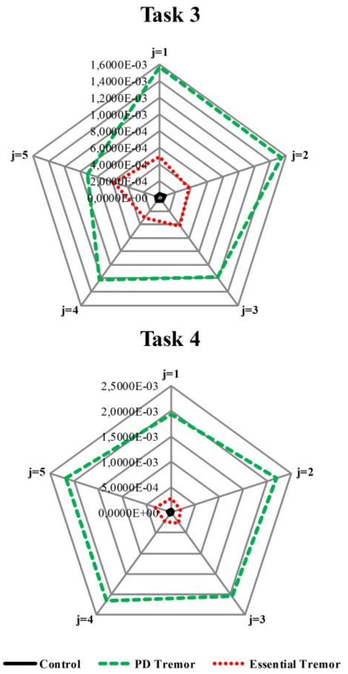

Fig. 3: Clockwise representation of the time evolution of changes in tremor for each group for the loaded tasks (task 3 and 4).

Additionally, Kruskal-Wallis tests were performed comparing the values of |m-b| between the three groups, see Table 1. Significant differences were only found for task 3 (p=0.036), for which Mann-Whitney U tests were performed to compare the groups two by two, see Table 2. Significant differences were observed between the control group and the dominant PD group (p=0.030).

Table 1. Kruskal-Wallis test results

	Task	
	3	4
χ^2_{KW}	6,656	3,548
p	0,036	0,170

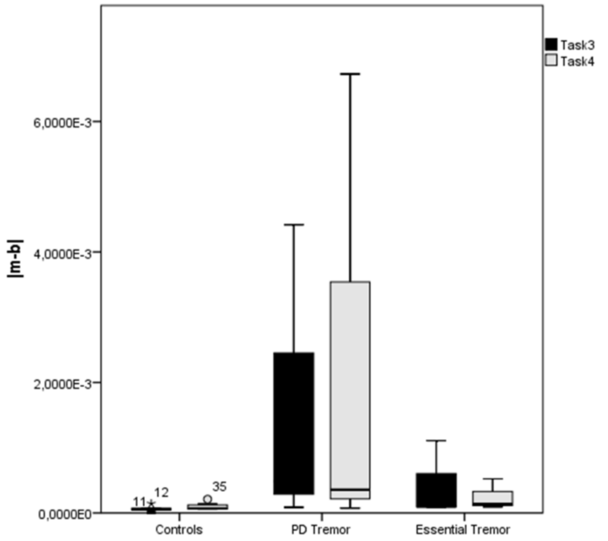

Fig. 4: Boxplot representing the absolute values of m-b for each group, for the loaded tasks (task 3 and 4).

Table 2. Mann-Whitney U test results for task 3

Groups	Control	Dominant PD
PD	0,030	-
ET	0,053	0,827

IV. Discussion

The goal of this work was to assess four tasks which modulate tremor to allow designing an efficient fMRI protocol for the identification of the cortical circuits associated to tremor in PD and ET. It follows a previous work from our group, where patients had been asked to repeat a movement where they would raise their arms for 30 sec and then return them to a baseline position for an equal period of time, cf. [8]. This was performed with and without added load. Significant statistical differences between the tremor profiles of the groups were found only for the unloaded task. However, radar charts showed for both tasks that the profiles corresponding to the dominant arms of the patients were visually very distinct, much like what is now shown in the present article for the loaded tasks (see Figure 3). A point in common between both articles is that the statistical differences are found between the control group and other groups (in the present article, only between controls and PDs, while a p value slightly greater than 0.05 was found when comparing controls and ETs). It was not possible to statistically distinguish PD's and ET's. The boxplot in Figure 4 illustrates why: the values of |m-b| are rather small for controls and can be much higher for PDs, but there is an overlap between the range of values attained by PDs and by ETs. This suggests that an fMRI protocol designed with one of the tasks that are examined here will only be useful to compare PDs or ETs to controls, and not the two patient groups between themselves. Note however that there were no ineligibility criteria for the volunteers who performed these tasks in terms of medication use or stage of disease. A selection of participants taking that into account should decrease the range of values of |m-b| for each group. Whether that will be enough to diminish the overlapping region in Figure 4 sufficiently so that statistically significant differences between the groups is attained may not be answered without performing more studies. Naturally, increasing the number of participants will also contribute to that.

The profiles displayed in Figures 2 and 3 suggest that performing tasks with added loading may contribute to clearing out a distinction between the profiles of tremor modulation for PDs, ETs and controls as it has been reported in the literature [10].

V. CONCLUSIONS

Patients were asked to perform tasks involving rapid arms motions. Our results show that placing an added load on the wrists of subjects interfered with tremor modulation in a way that allowed better discrimination between healthy controls and patients diagnosed with PD or ET. However, no statistically significant differences between the tremor measures associated to the two diseases were not found. The authors believe this to be due to the heterogeneity of patients and the small number of participants.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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