35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Tremor modulations across periods with and without voluntary motion and limb load task demands using movement quantification*

Paula Faria, Miguel Patrício, Gregor Philipiak, Francisco Caramelo, Cristina Januário, António Freire and Miguel Castelo-Branco

Understanding the neurobiological mechanisms underlying different types of tremor and the altered functional connectivity of the involved areas is a timely goal in clinical neuroscience. If successful, this quest may open new perspectives on how to achieve tremor modulation, which is notably relevant, in Parkinson's disease (PD). Tremor can be characterized by simple parameters such as frequency and amplitude. It is therefore prone to be objectively targeted by neuromodulation and quantitatively investigated using multimodal techniques, such as, accelerometry, EMG and functional Magnetic Resonance Imaging (fMRI). Embarking on the latter challenge requires an a priori knowledge of how effective functional connectivity is altered in PD tremor. This works aims to ascertain which postural and voluntary movement tasks with distinct types of physical load are suitable for designing efficient fMRI protocols, by performing an accelerometry analysis to measure spontaneous and imposed tremor modulation on cohorts of PD patients, essential tremor patients and a group of voluntary healthy controls.

I. Introduction

Tremor is a manifestation of different neurodegenerative diseases such as Parkinson's disease (PD). It is related to a progressive loss of dopamine neurons in the nigrostriatal system [1] leading to widespread motor symptoms (bradykinesia, rigidity, tremor and impaired balance) and cognitive impairments [2-3]. Although the diagnosis of PD remains clinical, advances in functional and structural imaging have improved the capacity to differentiate between PD and essential tremor, and between different akinetic-rigid syndromes [4]. As the distinctive neurophysiological pathways of Parkinson tremor have been surprisingly difficult to decipher [4-8], this work proposes to find the behavioral triggers of tremor to set the laying foundations for subsequent studies of its neural genesis.

Although some studies have explored tremor modulation when performing certain types of tasks (for example, pointing and grip tasks, entrainment, tapping, wrist extension, different loads weights [9-13]), in this work we plan to understand which type of upper limb movement positions, such as, relaxing, postural postures, ascending or descending upper limbs movements, with or without a 0.5 kg wrist load, is able to interfere with tremor. The frequency and amplitude of tremor modulations are compared across periods with and without, both, voluntary calibrated motion and limb load, in PD and essential tremor (ET) patients and a cohort of healthy controls using movement quantification (accelerometry analysis). Our results might allow to better design fMRI protocols which might be able to interfere with tremor modulation in order to gain some insight about the neural pathophysiology of tremor.

II. Methods

A. Subjects

Seven patients (aged 69.3 ± 8.4 years: 4 males and 3 females) participated in this study. All attend movement disorders consultations at the Coimbra University Hospitals. Four patients have been diagnosed with PD (aged 67.8 ± 8.8 years) and three with essential/postural tremor (aged 71.3 ± 9.3 years) by experienced neurologists who were trained in the differential diagnosis of tremor disorders (Hoehn & Yahr: I-III). Patient's medication was not modified before the tremor recordings. Only one PD presented a symmetric tremor, all others exhibited an asymmetric tremor prominent at the right upper limb [14]. All essential/postural tremor (ET) patients showed an asymmetric tremor which was prominent at the upper left limb. Seven healthy controls with no neurological abnormalities (aged 49 ± 18.3 years; 5 males and 2 females) were recruited on a volunteer basis from the local community. All participants were right-handed by self report. This study and all the procedures were reviewed and approved by the Ethics Commissions of the Faculty of Medicine of the University of Coimbra and was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all the participants.

B. Procedures

All study participants were asked to perform two identical and subsequent arm movement tasks (loaded vs. unloaded). The first task was load free, whereas in the latter loads of 0.5 kg each were placed in each of the participant's wrists. Each task had the duration of 6 min 20 sec and was composed by 21 segments where the subject had to place his arm in a prescribed position. The participants were guided trough the experiment by an animation programmed using

* Research supported by Centre for Rapid and Sustainable Product Development (CDRSP), School of Technology and Management (ESTG) of the Polytechnic Institute of Leiria (IPL), Portugal and Institute of Biomedical Research in Light and Image (IBILI), University of Coimbra (UC), Portugal.

Paula Faria is with the CDRSP, ESTG-IPL and IBILI, Portugal (corresponding author to provide phone: 00351-244569441; fax: 00351-244569444; e-mail: paula.faria@ipleiria.pt).

Miguel Patrício, Gregor Philipak, Francisco Caramelo and Miguel Castelo-Branco, are with IBILI, Faculty of Medicine of the University of Coimbra, Portugal, (e-mail: mjpd@uc.pt, gphilipiak@gmail.com, fcaramelo@ibili.uc.pt, mcbranco@fmed.uc.pt, respectively).

Cristina Januário and António Freire are with Faculty of Medicine and Coimbra University Hospital Centre (CHUC), Coimbra, Portugal (e-mail: cristinajanuario@gmail.com, afreireg@hotmail.com, respectively).

Physicophysics Toolbox Version 3, a free set of Matlab R2010a. Two balls each representing one arm, were initially placed on the bottom of a 33,8 cm x 27,1 cm computer screen (1280x1024 pixels). Each participant had to follow the balls movement with both arms. Different ball colors (blue and red) and screen positions (left and right, respectively) were chosen to represent the two arms (left and right, respectively). Each task started with the balls positioned, for 30 sec, in a black line localized at the bottom of the computer screen (i.e. arms placed along the body - *baseline position*). Then the balls started an ascending 5 sec movement (i.e. arms going up - *up position*). Afterwards, the balls remained for more 30 sec in a black line placed at the top of the computer screen (i.e., the positions of both arms were at a shoulder flexion of 90º with the elbow at full extension and forearm pronation, i.e., *top position*). Subsequently the balls started a descending 5 sec movement back to the baseline position (i.e. arms descending to the baseline position – *down position*) and the entire procedure would have to be repeated five more times for each of the two tasks (unloaded vs. loaded). The protocol for both tasks is illustrated in Fig. 1. Each task was explained carefully to the participants in order to avoid misunderstandings. In each task, participants were individually tested in a quiet room with normal daylight while seating in a comfortable heavy chair at a distance of 1 m from the computer screen.

Tremor modulations during arm movement were measured using two 3 axis accelerometers per participant. Two in-house built sensor modules were used, incorporating each a Kionix KXTF9 3 axis accelerometer with sensitivity of 8 bits/64counts/g, and a configured maximum rating of ± 2 g. The modules were attached in the dorsal part of both left and right hand near the fingers junctions. Acceleration data was sampled at 25 Hz and stored on a MicroSD for off-line analysis using Matlab R2010a.

C. Data processing and statistical analyses

An offline data analysis was performed using the absolute values of the 3D accelerations that were measured as a function of time. The frequency and amplitude of each acceleration function, were obtained for each arm of each patient, and each task, performing a Fourier analysis (Pwelch function) of the signals derived from accelerometry, following a band-pass filter (cut-off frequencies: 0-2 Hz). The amplitude as a function of the frequency was then integrated for each task segment using trapezoidal integration ([11]) and normalized to the corresponding duration. Though, the area under the curve between two vertical straight lines, which define each of the 21 moments of each task, was obtained. This resulted in a total of 21 scalar values being obtained for each patient's arm and each task. These values are hereby denoted by b_i, u_j, t_j and d_j (i ranging from 1 to 6 and j from 1 to 5), corresponding to the baseline, up, top and down positions, respectively. Four groups of data were then considered, pertaining to the dominant and the nondominant arms of the PD and ET patients - the PD patient who had a symmetric tremor, had to be rejected for the sake of the analysis. The corresponding data for the control group was averaged for both arms. All calculations were performed using Matlab R2010a.

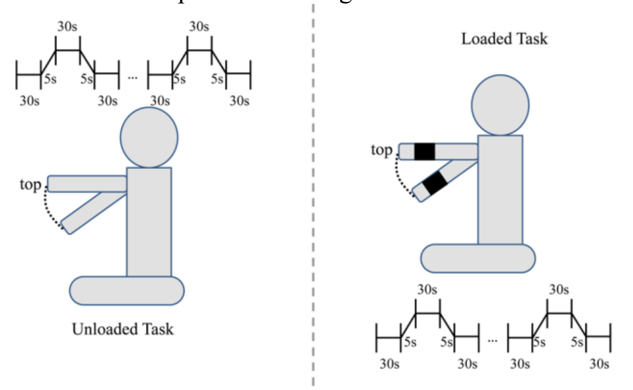

Figure 1. Schematic diagrams of task 1 (unloaded – left) and task 2 (loaded – right). Both tasks protocols are ilustrated on the figure, differing only by the 0.5 kg loads placed on the pacients wrists on the second task. Patients were seating down at all times. Each task was started with arms in the baseline position for 30 seconds (placed along their body). This was followed by raising both arms for 5 seconds (up position) until the top position was reached (at which the arms should be at a 90º elevation). The arms were to stand at the top position for 30 seconds. Finally, both arms were to perform a descending movement lasting a total of 5 sec (down position) back to the baseline position. The procedure was repeated for each task until the arms finally rested for 30 seconds in the baseline position, lasting a total of 6 minutes and 20 seconds per task.

To assess whether the actions within each task (laying arms at the baseline position, raising arms, keeping arms raised and lowering arms) had a different impact in the five groups of the study, the absolute values of u-b, t-b and d-b (where b, u, t and d are the averaged baseline, up, top and down values, respectively) were computed for each subject and compared between groups using Kruskal-Wallis tests followed by post-hoc Mann-Whitney U tests. All statistical analyses were performed with the IBM SPSS Statistics 19.0 software package assuming a 0.05 level of significance

III. RESULTS

Both groups of patients displayed a peak of frequency from 4 Hz to 7 Hz for both tasks as reported in the literature ([6, 8, 15]). A careful visual observation of the peaks of frequency could not detect any difference between the loaded and the unloaded tasks. Similar results were found in [16].

A global visualization of the time evolution of changes in tremor, between baseline and top positions, for both unloaded and loaded tasks, is represented by the radar charts presented in Fig. 2. For each group, the values of $|t_j\text{-}b|$ are represented clockwise in g^2. For both tasks the line corresponding to the control group is not visible due to the small magnitude of the corresponding values.

As the ranks of the values of $|t_j\text{-}b|$ for each group display little variation with the value of j, the data was further reduced by averaging the values corresponding to the top position. A Kruskal Wallis test was employed for each task to compare whether the absolute value of t-b varies between the groups, see Fig. 3 for a boxplot illustration. Significant intergroup variations were observed for the unloaded task

($\chi^2_{KW}(4)$ = 11,955; p =0,018) but not for the loaded task ($\chi^2_{KW}(4)$ = 7,405; p =0,116).

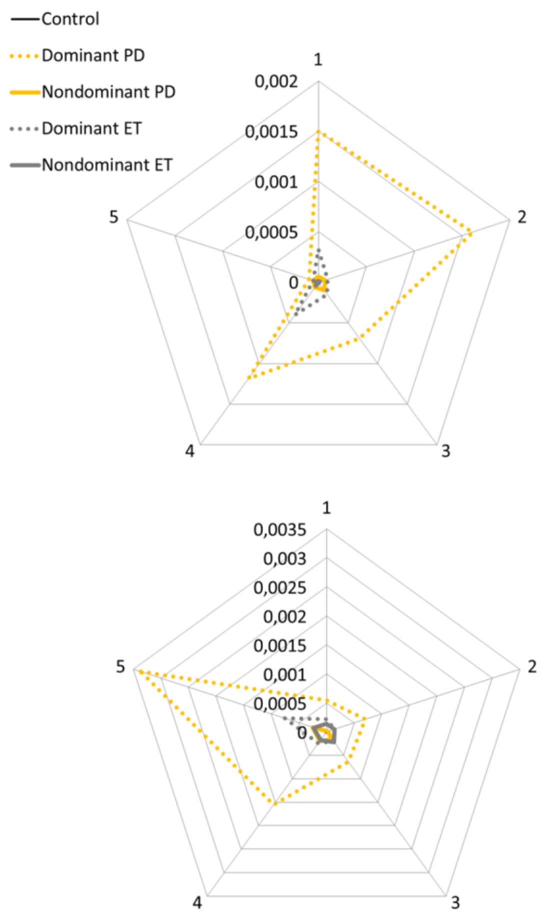

Figure 2. The absolute variation from the averaged baseline value to the time varying top position values $|t_j\text{-}b|$ are represented clockwise for the five groups and for both the unloaded (top figure) and loaded tasks (bottom figure). The five different segments are represented clockwise and the respective value of j has been included in the figure.

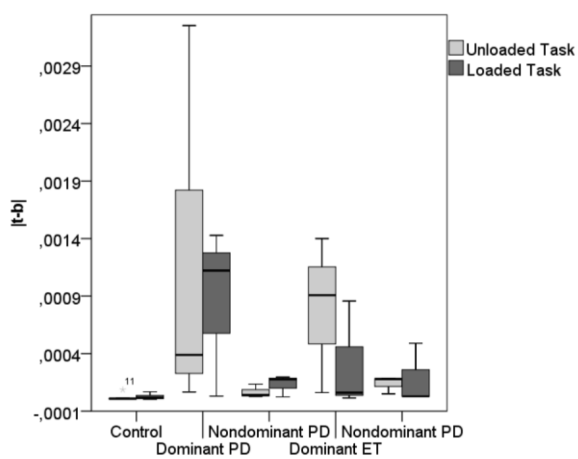

Figure 3. The absolute value of t-b is represented for the five groups and for the unloaded task (light gray) and loaded task (dark gray). Significant statistical differences between the groups were observed for the unloaded task only.

Post hoc Mann-Whitney U tests were used to further investigate the significant results for the unloaded task and are included in Table 1. Significant differences were observed between the control group and all other groups except for the nondominant PD.

TABLE I. MANN-WHITNEY U TEST RESULTS

Groups	**I**	**II**	**III**	**IV**
II	0,030	-	-	-
III	0,053	0,127	-	-
IV	0,030	0,827	0,127	-
V	0,030	0,275	0,127	0,275

Figure 4. Two-by-two comparisons between the five study groups (I – control; II – Dominant PD; III – Nondominant PD; IV – Dominant ET; V – Nondominant ET). The p-values of the post hoc Mann-Whitney U test comparison between groups are displayed.

Kruskal Wallis tests were also employed for each task to assess the intergroup variation of the absolute values of u-b and d-b. No statistically significant results were observed.

IV. DISCUSSION

Data arising from tasks performed by two cohorts of tremor-afflicted patients and a group of healthy controls was examined with the goal of shedding light on how the quantification of tremor using accelerometry may provide the tools to achieve tremor modulation. The study subjects comprised PD patients with a right upper limb dominant tremor, ET patients with a left upper limb dominant tremor as well as the control group. All participated as volunteers in two tasks, where they had to perform arm motions as requested. The first task differed from the second only in loads of 0.5 kg each being placed on the wrists of the volunteers. By understanding how motion and load characteristics interfere with tremor a protocol for future fMRI studies may be defined.

We started by looking at how differently the tremor responds to having to perform the physical tasks of raising arms, lowering arms or keeping them on horizontally parallel to the ground in PD and ET patients and a healthy control group. After normalizing the data by subtracting the baseline tremor it was possible to obtain the results displayed in Figure 2. This shows how for both the unloaded and loaded tasks it was the dominant arms of the patients that had higher variations in tremors due to the motion of the arms. A statistical significant result was obtained by comparing, for the unloaded task, both groups of the dominant arms with the controls: the former groups showed a greater increase in tremor amplitude. Unfortunately the same did not hold true for the loaded task: no significant results were found, in spite of the appealing bottom plot in Figure 2. The boxplots in Figure 3 provide much of the justification for this: the fact that no statistical significance is found is due to the variance in the dominant groups, which is likely due to the effects of the medication on the patients, which can have an impact in tremor measures of 25%-30% ([10, 17, 18]) and possibly contributed to a tremor decrease in some of them and had a role in compromising the homogeneity of the groups. Taking this point of criticism into account might suggest that the loaded task should not be discarded from fMRI protocols if the patient's medication is taken into account. Interestingly the loaded task seems to present a trend in Figure 2: the differences between the baseline tremor and the top position tremor are larger when the number of repetitions of the motions is greater. This pattern is not clearly repeated in the unloaded task. Though this is to be expected as the loads would tire the subjects, it should be investigated further.

No results with statistical significance distinguishing the study groups were found for the ascending and descending upper limbs movements in any of the tasks. This might be explained by the fact that tremor is inhibited during movement and may reoccur with the same frequency when adopting a posture or even when moving [6, 8, 14].

V. Conclusion

This article focused on determining which tasks interfere with tremor modulation, with significant difference in tremor being found between baseline position and top position. No significant evidence was found that placing weights on the patient's writs is capable of influencing tremor as reported also in ([16]) although we believe that may change if more tremor-wise homogenous groups of patients are considered. Building upon this insight will allow discussing, setting up and implementing a protocol for fMRI studies of the causes of tremor.

Acknowledgment

We are grateful to David Ribeiro at IEETA, University of Aveiro, Portugal, for the home made accelerometers built and for the technical support on the experimental acquisition of data.

References

[1] Hornykiewicz O "Biochemical aspects of Parkinson's disease", Neurology, 51(2), (suppl 2): S2-S9, 1998.

[2] Castelo-Branco M, Mendes M, Silva F, Massano J, Januário G, Januário C, Freire A., "Motion integration deficits are independent of magnocellular impariment in Parkinson's disease", Neuropsychologia, 47(2), pp. 314-20, 2009.

[3] Deuschl G, Bain P, Brin M, ", "Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee.", Mov Disord, 13 (Suppl. 3): S2-S23, 1998.

[4] Stoessl AJ, Martin WW, McKeown MJ, Sossi V, "Advances in imaging in Parkinson's disease", Lancet Neurol., 10(11), pp. 987-1001, 2011.

[5] Hellwig B, Haussler S, Schelter B, Lauk M, Guschlbauer B, Timmer J, et al., "Tremor-correlated cortical activity in essential tremor", Lancet, 357, pp. 519-23, 2001.

[6] Bergman H, Deuschl G, "Pathophysiology of Parkinson's Disease: From Clinical Neurology to Basic Neuroscience and Back", Mov Disord, 17 (3), pp. S28-S40, 2002.

[7] Raethjen J, Deuschl G, "Tremor", Curr Opin Neurol, 22, pp. 400-5, 2009.

[8] Massano J, Bhatia K, "Clinical Approach to Parkinson's Disease: Features, Diagnosis, and Principles of Management", Cold Spring Harb Perspect Med, doi: 10.1101/cshperspect.a008870, 2012.

[9] Jankovic J, Schawartz KS, Ondo W, "Re-emergent tremor of Parkinson's disease", J Neurol Neurosurg Psychiatry, 67, pp. 646-50, 1999.

[10] Brown P, Corcos DM and Rothwell JC, "Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease?", Brain, 1997, vol. 120, pp. 401-408.

[11] Schwingenschuh P, Katsching P, Seiler S, Saifee T, et al, "Moving Toward "Laboratory-Supported" Criteria for Psychogenic Tremor", Mov Disord, 26 (14), pp. 2509-15, 2011.

[12] Prodoehl J, Planetta PJ, Kurani AS, Comella CL, Corcos DM, Vaillancourt DE, "Diffenreces in Brain Activation Between Tremor- and Nontremor-Dominant Parkinson Disease", Arch Neurol, doi:10.1001/jamaneurol.2013.582, 2013.

[13] Hwang I, Lin C, Wu P, "Tremor modulation in patients with Parkinson's disease compared to healthy counterparts during loaded postural holding", J Electromyography Kinesiol, 19, e520-28, 2009

[14] Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BB, "Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits", Brain, 135, pp. 3206-26, 2012.

[15] Buijink AWG, Contarino MF, Koelman JHTM, Speelman JD, Rootselaar AF, "How to tackle tremor – systematic review of the literature and diagnostic work-up", Frontiers in Neurology doi: 10.3389/fneur.2012.00146,2012.

[16] Meshack RP, Norman KE, "A randomized controlled trial of the effect of weights on amplitude and frequency of postural hand tremor in people with Parkinson's disease", Clin Rehabil, 16, pp. 481-92, 2002.

[17] B. Hellwig, P. Mund, B. Schelter, B. Guschlbauer, J. Timeer, C. H. Lucking, "A longitudinal study of tremor frequencies in Parkinson's disease and essential tremor", Clinical Neurophysiology, 2009, vol. 120, pp. 431-435.

[18] Budzianowska A, Honczarenko K, "Assessment of rest tremor in Parkinson's disease", Neurologia I Neurochirurgia, 42 (1), pp. 12-21,2008.