Visualisation of Parkinsonian, essential and physiological tremor planes in 3D space

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Summary

Based on the fact that tremors display some distinct 3D spatial characteristics, we decided to visualise tremor planes in 3D space. We obtained 3-axial linear accelerometer signals of hand tremors from 58 patients with Parkinson´s disease (PD), 37 with isolated resting tremor (iRT), 75 with essential tremor (ET), and 44 healthy volunteers with physiological tremor (Ph). For each group analysis was done with subsequent spatial 3D regression of the input data i.e. along the *x*, *y* and *z* axes; the projected vector lengths in the individual (vertical transversal *XY*, vertical longitudinal *XZ* and horizontal *YZ*) reference frame planes and their angles. Most meaningful and statistically significant differences were found in the analyses of the 3D vector lengths. The tremor of the PD and the iRT group was oriented mainly in the horizontal *YZ* plane. The tremors of the patients with ET and Ph were oriented approximately in the midway between the all three referential planes with less tilt toward the vertical longitudinal *XZ* plane.

Key words: 3-axial linear tremor accelerometry; analysis of tremor plane in 3D space; Parkinsonian tremor; essential tremor; physiologic tremor

Introduction

Among the myriad neurological disorders associated with tremor, Parkinson's disease (PD) and essential tremor (ET) are the most common (Benito-León and Louis 2006, Louis *et al.* 2009, Campenhausen *et al.* 2005, Wirdefeldt *et al.* 2011, Louis and Ferreira 2010). The clinical distinction between these entities is quite easy in the case of fully-developed Parkinsonism (Bhidayasiri 2005, Thenganatt and Louis 2012, Vidailhet *et al.* 2017). On the other hand, a significant proportion of PD patients may present with a monosymptomatic tremor which can precede the other signs of the disease by many years (Chen *et al.* 2017, Ghaemi *et al.* 2002). In such cases the clinical distinction is a rather difficult task. Most of the instrumental techniques for tremor assessment have focused on the frequency domain of the EMG and/or accelerometry data (Ghassemi *et al.* 2016, Farkas *et al.* 2006, Cichaczewski *et al.* 2016, Ruonala *et al.* 2013, Wilk and Olbrycht 2016). Little is known about the trajectories and the spatial aspects of the tremor. However, as we have shown recently, that some tremors, namely the Parkinsonian resting tremor and the mono-symptomatic resting tremor can also display distinct measurable 3D spatial characteristics (Jombik *et al.* 2018). One important aspect of tremor analysis in the 3D space is that by our previously published method we could reliably calculate only the apparent projections of vector lengths and orientations into the arbitrary experimental reference frame, i.e. the view analogous to the Chinese shadow theatre. Thus, we can exactly calculate the length of the true spatial vector but not its orientation. However, the 3D regressions could display the dominant tremor plane in the space. For this study we decided to show the main differences in the tremor planes in 3D space and visualize them for better comprehension of these tremors.

Methods

Patients

The study was performed in accordance with the ethical standards of the responsible committees for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all study participants.

We assessed a total of 170 patients with a hand tremor, divided into three groups according their clinical diagnosis, which was made by an expert in the field of movement disorders (J.N.). The first group consisted of 58 patients with clinically definite PD (according to the MDS clinical diagnostic criteria for PD (Postuma *et al.* 2015)), so they were named the Parkinsonian tremor (PT) group. The second group consisted of 37 patients with isolated resting tremor (iRT), in which the tremor was mostly asymmetric and present in the resting position. This type of tremor was often virtually identical with the resting tremor in PD, however these patients did not show any other clear signs of Parkinsonism (e.g. rigidity or bradykinesia) or other movement disorder at the time of the study. Seventy five patients with ET with bilateral action tremor of the hands diagnosed according to criteria from Bhatia *et al.* 2018 formed the third group. Patients with possible tremors of other etiology (e.g. dystonic tremor, medication-induced tremor etc.) as well as with obvious leg tremor were excluded from the study. The findings in the above-mentioned pathological tremor groups were compared with the findings of 44 healthy volunteers forming the physiological tremor (Ph) group. The basic characteristics of all 353 examined hands are summarized in Table 1.

Recording procedure

We used a custom-made tri-axial linear accelerometer made from two ADXL320 dual-axis analog devices cemented together to record the linear acceleration of the hands. The accelerometer was fixed to the back of the hand at the centre of the third metacarpal bone. The axes of the hand were established under these rules: the antero-posterior (wrist-fingers) as *"z"*, the vertical (dorsum of hand-palm) as *"x"* and finally the transversal (radial-ulnar) as *"y"* axis. These three axes created the three planes of the hand referential frame (vertically-oriented transversal XY plane, vertically-oriented longitudinal XZ plane, and horizontal YZ plane). A schematic drawing of the reference system is shown in the Figure 1. For recording of the resting tremor, patients were seated and the hand was placed on a foam block put on the horizontally-positioned thigh. For recording of the postural tremor the arms were held in the outstretched position. All patients as well as the control subjects were instructed to avoid doing any voluntary movements. EMG signals were recorded by surface electrodes from the extensor carpi radialis muscle. The signals from the accelerometer and EMG were amplified and band-pass filtered 0.5-50 Hz and 10-100 Hz respectively, at 200 Hz sampling rate (Neuro-Mep; Russia). The accelerometer was calibrated (0.4 mV for 2g acceleration) and the accelerometer data were transformed to acceleration units in $mm.s^{-2}$. Just before recording of each individual patient the hand movements were tested whether they are in accordance with the x, y and z axes. Subsequently, two recordings of resting tremor and one recording of postural tremor were made from each hand. The recording time of each recording was 60 s.

Data analysis

The time series of the accelerometer signals were subjected to off-line vector analysis using a custom-made mathematical program in Excel. Firstly the accelerometer data (i.e. voltage values) were converted into acceleration values in $mm.s^{-2}$. The length of the common spatial vector was calculated for each data point of the time series according to formula 1. From the two recordings of the rest tremor in each subject the stronger tremor (showing higher average common vector length value) was selected for further analysis. The lengths and the angles of the common spatial vector projection to the *XY*, *XZ* and *YZ* reference frame planes were calculated according to formulas 2-3. For angle calculation, the pairs of the accelerometer data rows were assigned as the real and the imaginary coefficients of the complex number (e.g. x + yi). Then, from the complex numbers the imaginary arguments were determined as the angles according to formula 3.

(1) $$|\vec{u}| = +\sqrt{a^2 + b^2 + c^2}$$

(2) $$|\vec{v}| = +\sqrt{a^2 + b^2}$$

(3) $$IMARGUMENT(z) = arctg(\frac{real(z)}{imag(z)})$$

The symbols a, b and c refer to general description of formulas.

Spatial 3D regression of the 3-axial accelerometer data along the *x*, *y* and *z* axes (formula 4), the projected vector lengths in the individual (*XY*, *XZ* and *YZ*) reference frame planes (formula 5) and their angles (a) (formula 6) were calculated for each individual recording, as shown below.

(4) $X = \mathrm{a} + \mathrm{b}*Y + \mathrm{c}*Z$

(5) $XY = \mathrm{a} + \mathrm{b}*YZ + \mathrm{c}*XZ$

(6) $\mathrm{a}XY = \mathrm{a} + \mathrm{b}*\mathrm{a}YZ + \mathrm{c}*\mathrm{a}XZ$

The symbols a, b, and c refer to formulas in the general description.

Intercepts, the *YZ*; *XZ* and the a*YZ*; a*XZ* slopes coefficients and the magnitude of the differences between the slopes (*YZ-XZ*; aYZ-aXZ) respectively for each subject were subjected to statistical analysis using Kruskal-Wallis ANOVA. The significance level was set at $p < 0.05$. The lumped data of each patient group and the control group were displayed in 3D surface plots using Statistica 10 software (Czech version).

Results

Resting tremor

In the 3D linear regression of the vector lengths computed according to the model $XY = \mathrm{a} + \mathrm{b}*YZ + \mathrm{c}*XY$, the slopes in most of the PT patients and in patients of the iRT group showed a positive coefficient for the vector lengths in the *YZ* plane and a negative coefficient for the vector lengths in the *XZ* plane. The majority of the ET patients and the control subjects showed positive values for both coefficients. Thus, in turn PT patients and the patients in the iRT group showed stronger vector separation than the ET patients and the control group. These differences were reflected in subtractions of the *YZ-XZ* vector slopes (Table 2, Figures 2 and 3). The differences in all the above-mentioned parameters between the PT and the iRT groups compared to the ET group and control group were significant at $p < 0.001$. The differences between the PT and the iRT groups were not significant. Moreover the differences between the ET and the control groups were not significant except for the *YZ* slope coefficient. Here the control group showed significantly lower values to the ET group at $p < 0.001$. The differences in the intercepts were mostly not significant. Less meaningful results with regard to the group separation were obtained in the linear 3D regression of the angles, except the *YZ-XZ* differences. PT and iRT groups showed significantly higher values than the ET and control groups. Moreover the angle differences were also significantly higher in ET than in the control group (Table 2 and Figure 3). Finally the regression of the values of primary data of the accelerometer axes did not reveal any significant differences between groups.

Postural tremor

In most of the above-mentioned parameters only the control group showed significant differences to the rest of the tested subjects. The differences between the PT, iRT and the ET groups were not significant. For conciseness and clarity we present here only the findings in the resting tremor vector lengths.

Discussion

We focused primarily on the nature of the tremor itself and its visualization in space. To far as we know, they are no other similar publications focused on this aspect of tremors. In this study the influence of clinical stage, duration of the illness or effect of medication on tremor were not systematically investigated. We are aware of the mean age difference between the ET and Ph and the PT and iRT groups (Table 1). It could be considered as a limitation of the study. However, this difference did not influenced the severity or spatial characteristics of tremor.

The presented findings show significantly different orientation of the tremor plane in 3D space between the PT and the iRT patients in contrast to the ET patients and the control group. The major differences were in the vector length domain. The tremor of the PD and the iRT group was oriented mainly in the horizontal *YZ* plane with some tilt toward the vertical transversal *XY* plane and away from the *XZ* plane. The tremor of the patients with ET and Ph was oriented between the vertical transversal *XY* plane and the horizontal *YZ* planes and with a less but still significant contribution of the vertical longitudinal *XZ* plane. These findings are in agreement with another parameter of the tremor trajectory, i.e. the ratio of the *YZ* vector length to the common spatial vector length (*YZ/XYZ*) (Jombik *et al.* 2018). Thus these findings corroborate the hypothesis of the difference between the tremor trajectories in 3D space between some tremors with different pathogenesis. These differences are probably caused by different patterns of muscle activation in the time and space domains. The presented method showed less precise group separation in comparison with the *YZ/XYZ* ratio. The reason is in the higher variance. Coefficients of variation (CV) of *YZ/XYZ* ratio showed extraordinarily low values at or below 0.05. Thus, the higher CV of the presented date tend them less suitable for the routine clinical praxis. However, the method might be useful in detailed analysis of borderline cases. Moreover, its advantage lies in the graphical visualisation, which allows better comprehension of the tremor plane in space.

Figures legends:

Figure 1. Schematic drawing of the reference frame.

Figure 2. Surface 3D plots of the resting tremor based on model *XY* = a + bYZ* +**

c*XZ

The panels at the top show tremor planes in the Parkinsonian patients (on the left) and the iRT patient (on the right) groups. The panels at the bottom show tremor planes of the ET (on the left) and the control groups (on the right) respectively. The color scale reflects the results of the equation i.e. values of vector projections to the XY plane. The blue dots reflect the values of the common vector.

Figure 3. Box plots of the data showing statistically significant differences between the tremors.

The panels at the top show the values of *YZ* and *XZ* vector lengths slopes on the left and right respectively. The panels at the bottom show the *YZ-XZ* vector length differences and *YZ-XZ* angles (*aYZ-XZ*) differences on the left and right respectively.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

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Table1. Patient´s characteristics

	Subjects (*n*)			Hands	Age (*years*)	
	Female	Male	Total		Mean	SD
PT	36	22	58	78	68,7	8,7
iRT	24	13	37	37	62,2	11,2
ET	41	34	75	150	57,6	14,9
Ph	24	20	44	88	52,7	19,0

Table 2. Results of the vector lenght, *YZ-XZ* length differences and *aYZ-aXZ* angles differences 3D linear regression analysis in *XY*=a +bYZ*+ c**XZ* model**

PT						iRT				
	YZ	*XZ*	*YZ-XZ*	*aYZ-aXZ*			*YZ*	*XZ*	*YZ-XZ*	*aYZ-aXZ*
Mean	**1,0630**	**-0,4527**	**1,5157**	**1,5157**		**Mean**	**1,0595**	**-0,3980**	**1,4576**	**1,4576**
SD	0,0825	0,2227	0,2788	0,2788		**SD**	0,0866	0,1872	0,2416	0,2416
CV	0,0776	0,4918	0,1839	0,1839		**CV**	0,0817	-0,4705	0,1657	0,1657
Min	0,6577	0,9485	0,6109	0,6109		**Min**	0,8864	-0,8019	1,0419	1,0419
Max	1,2478	1,1476	2,1735	2,1735		**Max**	1,2978	-0,0417	2,0998	2,0998
ET						**Ph**				
	YZ	*XZ*	*YZ-XZ*	*aYZ-aXZ*			*YZ*	*XZ*	*YZ-XZ*	*aYZ-aXZ*
Mean	**0,7032**	**0,2184**	**0,5385**	**0,5385**		**Mean**	**0,6097**	**0,2018**	**0,4227**	**0,4227**
SD	0,1887	0,2687	0,3322	0,3322		**SD**	0,1309	0,1758	0,2301	0,2301
CV	0,2684	1,2306	0,6167	0,6167		**CV**	0,2147	0,8714	0,5444	0,5444
Min	-0,2725	-0,4503	0,0069	0,0069		**Min**	0,3082	-0,2234	0,0126	0,0126
Max	1,0000	0,9909	0,9909	0,9909		**Max**	0,8984	0,7791	0,9324	0,9324

The figures displayed in bold refers to mean values showing significant difference $p<0.001$ of the PT and the iRT groups to the ET and the control groups, but not significant differences between the PT and iRT groups and ET and control groups; Kruskal-Wallis ANOVA. *CV* coefficient of variation, *YZ-XZ* YZ-XZ difference, *aYZ-aXZ* YZ-XZ angles difference

Fig. 1:

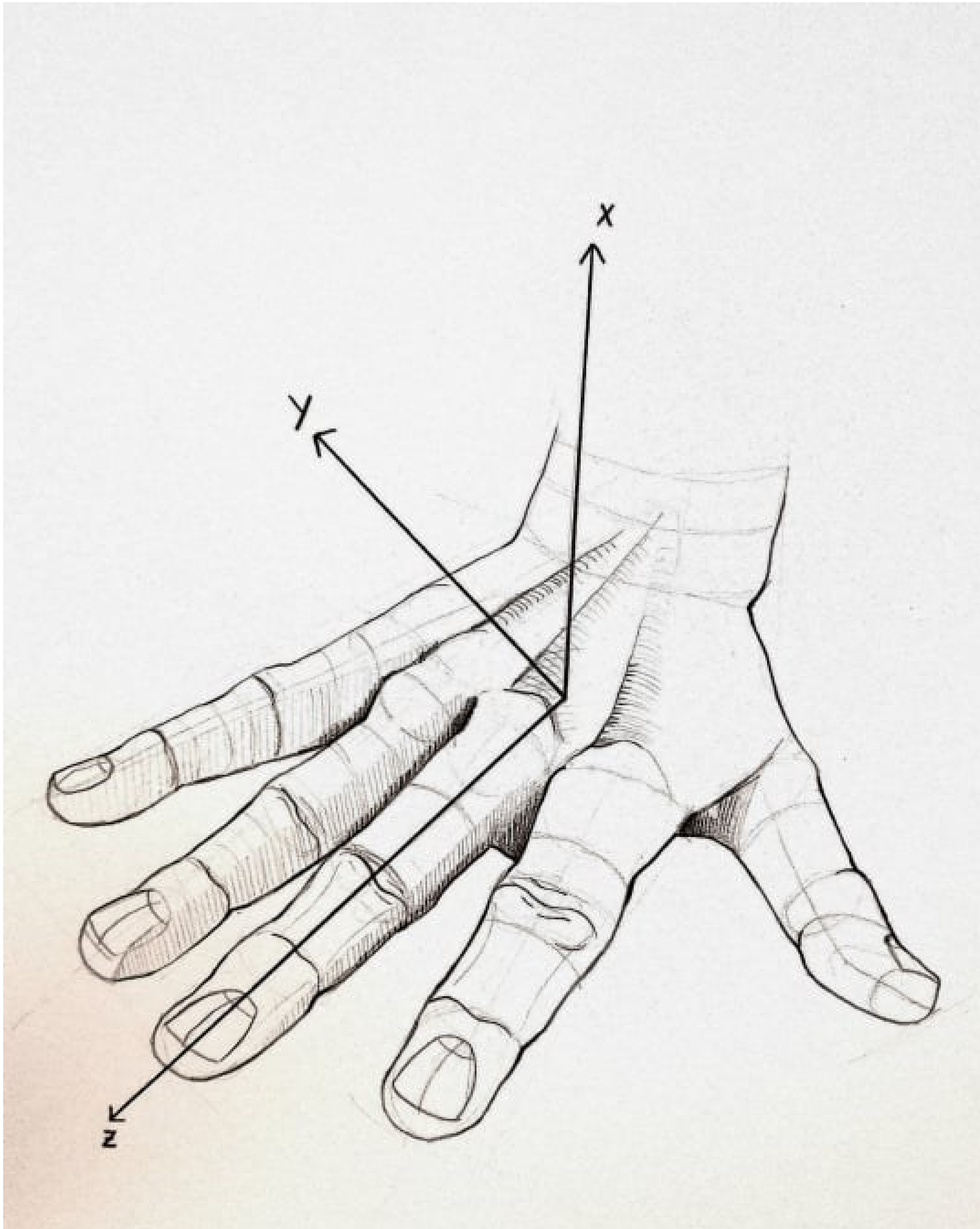


Fig. 2:

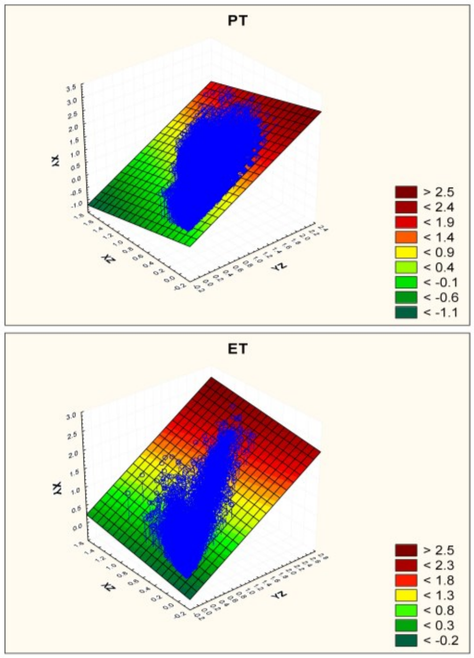
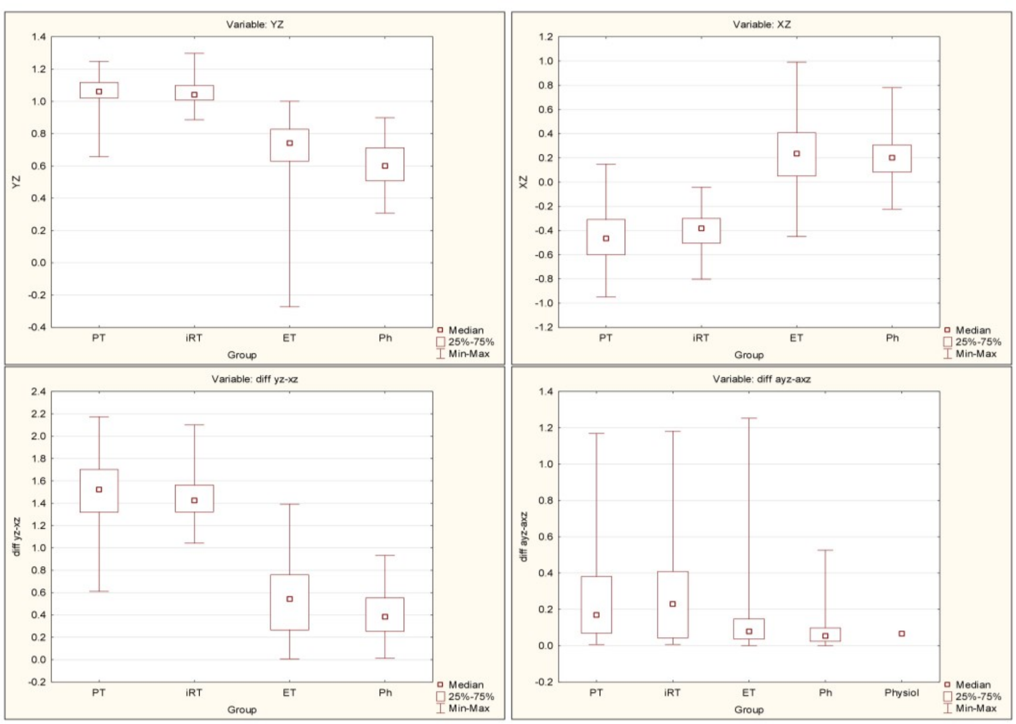

PT
> 2.5
< 2.4
< 1.9
< 1.4
< 0.9
< 0.4
< -0.1
< -0.6
< -1.1
iRT
> 5
< 4.5
< 3.5
< 2.5
< 1.5
< 0.5
< -0.5
< -1.5
ET
> 2.5
< 2.3
< 1.8
< 1.3
< 0.8
< 0.3
< -0.2
Ph
> 0.16
< 0.15
< 0.11
< 0.07
< 0.03
< -0.01

Fig. 3:


Variable: YZ
YZ
Group
PT
iRT
ET
Ph
Median
25%-75%
Min-Max
Variable: XZ
XZ
Variable: diff yz-xz
diff yz-xz
Variable: diff ayz-axz
diff ayz-axz
Physiol