Novel smart data analysis technologies to differentiate Parkinson's disease from essential tremor

Novel smart data analysis technologies to differentiate Parkinson's disease from essential tremor

A A Horoshavina[1], K O Tutsenko[1], V A Abramov[2], M E Tunik[1,2], D V Pokhabov[1,2] and M G Sadovsky[1, 3, 4]

[1] Krasnoyarsk State Medical University, Partizana Zheleznyaka, 1, Krasnoyarsk, 660022, Russia
[2] The Federal Siberian Research Clinical Center of FMBA of Russia, 26 Kolomenskaya St., Krasnoyarsk, P.O.Box 6213, 660037, Russia
[3] Institute of Computational Modelling SB RAS, Akademgorodok, 50/44, Krasnoyarsk, 660036, Russia

[4] E-mail: msad@icm.krasn.ru

Abstract. Smart approach to study the relation between tremor and olfactory malfunction is studied. It is shown that neither olfactory function measurement, nor tremor measurement solely are able to differentiate Parkinson's disease from essential tremor. On the contrary, the combination of these two medical examination techniques yields reliable discrimination of these two pathologies. Also, the inverse relation pattern between olfactory and tremor is proven. These results are obtained through the implementation of novel smart technique of non-linear clustering based on elastic map method.

1. Introduction

Parkinson's disease (PD) and essential tremor (ET) are among the most common diseases based on the extrapyramidal system malfunction. However, despite the developed clinical guidelines and the emergence of up-to-date diagnostic methods, misdiagnosis still is quite often in the differential diagnosis of these diseases [1]. The reason for that, as a rule, is a similarity in symptomatology. Tremor is the common symptom for these diseases. It is the core clinical manifestation in PD and ET and one of the leading complaints from patients visiting a doctor, since the tremor remarkably impairs the quality of life of such patients [1 – 3]. Additionally, problems in the differential diagnosis of these pathologies can arise at the early stages of their development, when the clinical manifestations are still minimal, or if a patient has symptoms of both diseases simultaneously [3, 4].

Errors in diagnostics lead later to therapeutic mistreatment, therefore, the success of treatment directly depends on the correct differential diagnosis. A start of therapy at the early stage of the development of these enhances its efficiency and slows down the progress of the disease. To ensure the possibility of early stage treatment, one needs an adequate diagnosis of these diseases among the people comprising a group at risk [5, 6]. Moreover, the correct diagnosis is also highly important from the point of view prognosis elaboration: ET is known for better prognosis in comparison to PD [1].

Rest tremor is a distinctive feature of PD; that latter significantly goes sown or disappears with active movements of a patient. On the contrary, ET is characterized by postural-kinetic tremor, which arises during movement of a patient and / or when the patient voluntary fixes himself in a certain posture [2].

Additionally, tremor in these diseases (in classical cases) differs in frequency, amplitude, type, inclusion of specific parts of body, etc. Thus, the determination of specific characteristics of tremor yields the proper recognition and distinguishes these two diseases [2 – 4, 7].

Besides the movement disorders, these pathologies have a number of non-motor symptoms, that also can be diagnostically important. Olfactory dysfunction in PD is among them. It has been found that olfactory malfunction in people with PD occur long before the onset of movement disorders [5, 6, 8 – 12]. This fact might have an apparent explanation: neurodegeneration starts precisely in the olfactory bulbs of brain. ET has another mechanism of development and, reciprocally, the patients with ET usually have no olfactory malfunction as a symptom [13]. Hence, olfactory dysfunction can both be an early diagnostic symptom of PD, and differentiate it from PD, as well as from other diseases with preserved sense of smell [10 – 12, 14, 15].

Everything said above unambiguously reveals that tremor data records in patients with PD and ET, together with their olfactory function records can contribute the correct diagnostics even at an early stage of the disease. However, the scientific evidences for the interplay between tremor and olfactory disorders are still insufficient. Thus, the aim of this work is to present the results of combined study of the olfactory function and the tremor in patients with PD and ET as a method of differential diagnosis of these diseases, as well as to approve the hypothesis on the inverse proportionality between the degree of smell impairment and the severity of tremor in these groups of patients.

2. Material and methods

An investigation of olfactory function was carried out using Sniffin' sticks test (Burghart Messtechnik, Germany) [16], with the determination of three indicators: threshold sensitivity, differential sensitivity and identification of a specific smell. The study was carried out at the Siberian Clinical Center of FMBA of Russia and in Krasnoyarsk state medical university. This is a common fact that Sniffin' sticks test consists of three subtests.

The first subtest (determination of smell perception threshold) was carried out the standard scheme. There are 16 triplets of three pens, one of them containing *n*-butanol: the triplets differ in the stuff concentration: the higher is the level, the lower the odorant concentration. A patient is instructed to identify a pen from three ones, which smells, from the point of view of the patient. Here the minimal concentration of odorant that the patient is able to distinguish from placebo must be detected.

The second subtest (odor discrimination) aims to examine the ability of a patient to detect given odor from two other ones. A patient is offered with 16 triplets so that each pen in a triplet contains different odorant. A patient is instructed to determine this peculiar odor.

The third subtest (odor identification) aims to examine the ability of a patient to identify the specific smell and chose the proper name from four options proposed by a tester. It consists of 16 pens with different smells. Following the standard protocol, the olfactory function of patients was estimated according to the results of all three subtests: maximal score in each subtest is 16 points, and the final score is the sum of the points recorded in all three subtests. The total score exceeding 30 indicates the norm, score from 17 to 29 points indicates hyposmia, and the score below 16 indicates anosmia. 45 patients with PD, 40 people with ET, and 64 conditionally healthy people (control group) have been examined.

Tremor parameters were measure by "*Colibri*" wireless instrument for monitoring of electrophysiological. Four sensors to measure the tremor have been used located on the wrists and forearms of both hands. Each registration module recorded three variables: surface electromyogram (EMG), rotation acceleration and linear acceleration. Both frequency and amplitude of each of the three indicators have been recorded. Remote recording allowed the registration both at rest and in motion. The study of tremor includes 5 tests, totally. The first test records the indicators in rest; the second test records the indicators from the patients standing Romberg's position with closed eyes and arms streched straight in front of them; the third and fourth tests record the tremor indicators from a patient standing still with close eyes and instructed to touched the tip of the nose with right and left hand, respectively;

the fifth test records the tremor characteristics in motion when patients moved around the room. Tremors were analyzed in 90 people: 30 conditionally healthy people and 30 PD patients and 30 ET patients.

Data analysis was done with IBM SPSS Statistics 23 software using classical statistical methods: determination of the mean, standard deviation, median and quartiles, Shapiro-Wilk test was used to check for normality of distribution, and Student's test and Mann-Whitney test were implemented to compare the obtained results. In addition, the data were processed by the nonlinear elastic maps method with freely distributed *VidaExpert* software.

3. Results

The olfactory function was examined in 45 patients with PD, 40 patients with ET, and 64 conditionally healthy people (control group). The control group comprised 33 men and 31 women aged 20 to 79 years. 15 men and 30 women aged 35 to 78 years old comprised PD patients group, and finally, 12 men and 28 women aged 22 to 82 years comprised ET patients group. The resulting scores obtained according to the standard research protocol are summarized and shown in table 1. For normally distributed data the table shows the mean values ± standard deviation, for the data with non-normal distribution it shows the median, 1st and 3rd quartiles.

Table 1. Results of examination of olfactory function, scores.

	Test 1	Test 2	Test 3	Total score, number of testees and their percentage		
	Av.score	Av.score	Av.score	Anosmia	Hyposmia	Normosmia
Control	5.11 ± 2.32	12 [10; 13]	11.28 ± 2.18	3 (4.7 %)	32 (50 %)	29 (45.3 %)
ET	4 [1.75; 6]	10 ± 2.65	10.5 [8.75; 12]	2 (5 %)	31 (77.5 %)	7 (17.5 %)
PD	2 [1; 4]	9 [7; 10]	6.87 ± 2.69	14 (31.1 %)	30 (66.7 %)	1 (2.2 %)

Further, all the data were tested for normality of the distribution using Shapiro-Wilk test; after that they were compared for each indicator. The statistical method for comparison has been chosen based on the normality of the distribution: if the data are distributed normally, then the comparison was carried out by the Student's test, on the contrary, Mann-Whitney test was used. Statistically significant differences were found between all groups of testees at the significance level $\alpha = 0{,}05$.

Thus, the classical methods of statistics showed that the data obtained in different groups of testees differ from each other. However, it is necessary to check how well these data are able to divide the people under examination into clusters and if so, whether the clusters comprise preferably the patients from each group individually (healthy people, people with PD and people with ET). To solve this problem, unsupervised clustering is used provided by nonlinear method of elastic maps [17, 18]. This method reduces the dimension of data and visualize it.

Figure 1 shows clustering of the patients provided over all 3 subtests. Here healthy people are marked in green, PD patients are marked in red, and ET patients are marked in blue. Figure 1A shows that each group tends to merge into a very tight cluster; this pattern clearly approves an invalidity of the 1st subtest for discrimination between the studied groups. The second subtest (figure 1B) and the third subtest (figure 1C) effectively distinguish the patients and control.

The results unambiguously approve that the procedure for determination of the olfactory threshold declared by the authors of the test is invalid and brings systematic error. The proof of this statement, as well as the description of the modernization of the protocol for the 1st subtest, are described in more detail in [19].

Also, few words should be said about the shortcomings of the third subtest, which aims to determine the ability of a patient to identify odors. Let's remind that the testees had to determine what kind of smell they felt through the choice of the correct option from the four proposed. Some of the smells suggested by the authors of the test are not suitable for this study in Russia. For example, the names of smells like "licorice", "turpentine" and "anise" are not familiar to everyone. To solve this problem and modify this subtest in future, further researches are necessary.

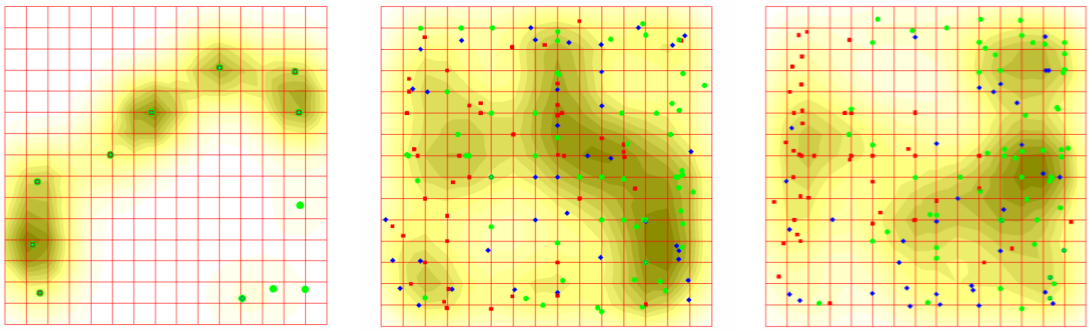

Figure 1. Elastic map showing the distribution over the first subtest (A), the second subtest (B), and the third subtest (C).

Besides the testing of the olfactory function, we also measured tremor among all the groups mentioned above. We tried to detect the differences in tremor indicators between the studied groups using standard statistical methods. Details of the results obtained can be found in article [20]. Since the number of indicators characterizing the tremor of patients significantly exceeds the number of indicators of the olfactory function (280 vs. 52, respectively), we tried to select the most informative ones. It should be said that such selection will greatly simplify both the collection of data and their processing.

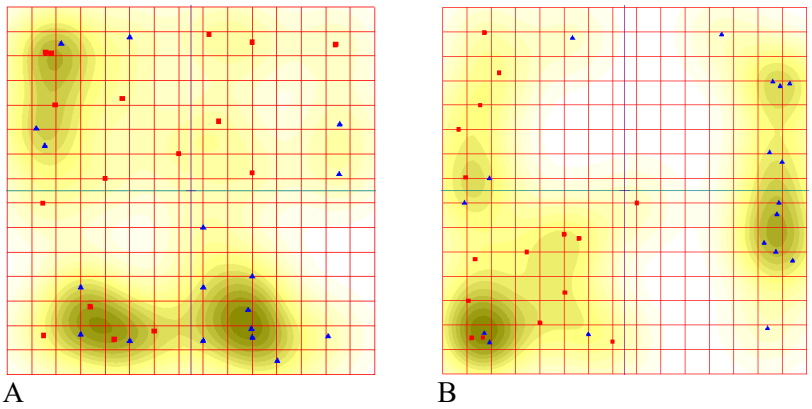

Figure 2. Distribution of PD vs. ET patients over the tremor (A) and over the combination of tremor and olfactory (B).

There are various ways to reduce the dimensionality of data, and principal component analysis (PCA) is number one here. We tried this method to all jitter indicators (except for indicators with zero variance). PCA brought no results: data on tremors make a kind of spherical pattern with no clear linear structuredness.

In such capacity, we have checked the distribution histograms for each of the tremor indicators and selected only those indicators whose histograms were the closest to the normal distribution, that is, unimodal and are bell-shaped. Next, an elastic map was developed, over the selected indicators of tremor (see figure 2A) only, and the map developed over the combination of olfactory measurement and tremor records tremors (see figure 2B). PD patients are shown in red squares, and ET patients are shown in blue triangles. These maps show that combination of the records of tremor and records of olfactory function results in good discrimination of the patients with different pathologies (see also figure 3).

At the next step we compared the indicators of people gathered into different clusters. The only reliable statistical difference between the first and the second clusters was found for the total score obtained in the 3rd olfactory subtest. This fact might be explained by the significant prevalence of PD

patients in these two clusters. Statistically significant difference was found between the first and third clusters, as well as between the second and third ones, expressed both in terms of tremor and in terms of smell. This fact makes a strong evidence of the difference between PD patients, and ET patients, if measured in terms of tremor and olfactory function. However, a reliable difference was found for gyroscope data, only.

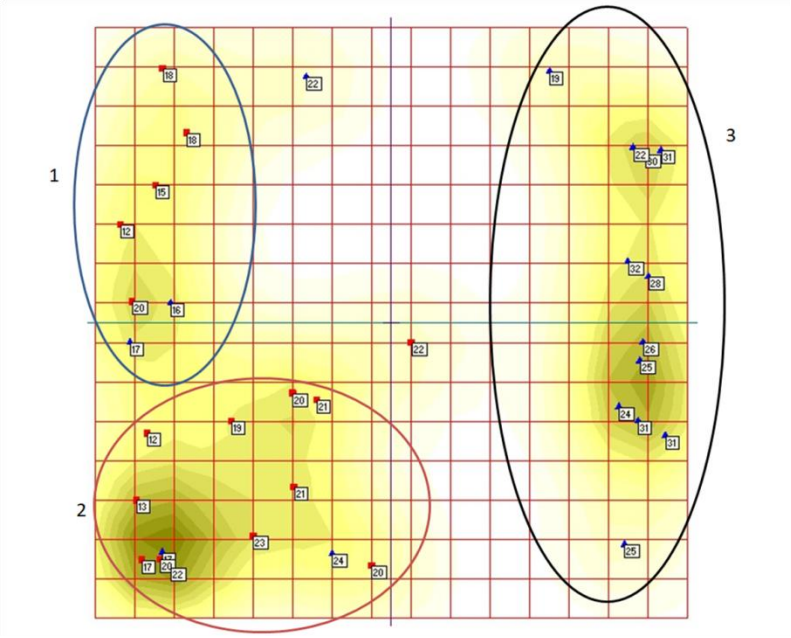

Figure 3. Clustering of PD patients vs. ET patients.

Analysis of the quantitative evaluation of olfactory function shows that patients in cluster 3 (people with ET) have better sense of smell than the patients in clusters 1 and 2. Thus, it confirms the hypothesis on the inverse relation between the severity of tremor and the degree of smell dysfunction. We suppose the patients with ET falling into clusters 1 and 2 have less favorable course of the disease, since it is known that some patients with ET meet cognitive and affective complications, and the severity of tremor decreases [3].

Thus, the combination of the data of olfactory function and essential characteristics of tremor in examination of patients with PD and ET can significantly increase the accuracy of differential diagnosis of these diseases and support correct diagnostics both at the onset of the disease and in complicated clinical cases. In addition, the study of these characteristics is valuable from prognostic point of view making better planning of a planning a treatment strategy for a patient, in the long term.

References

[1] Trufanov Y O 2013 *Medicinskij vestnik Yuga Rossii.* **1** 73-9 (In Russ.)
[2] Govorova T G, Tappakhov A A, Popova T E and Antipina U D 2018 *Consilium Medicum.* **20(9)** 95-100 (In Russ.)
[3] Ivanova E O, Fedin P A, Brutyan A G, Ivanova-Smolenskaya I A and Illarioshkin S N 2013 *Nevrolgicheskii zhurnal* **18(5)** 21-6 (in Russ.)
[4] Titova N V, Bezdolny Y N, Shtuchny I V and Sibetsky D A 2019 *Meditsinsky Sovet*. **9** 46-54
[5] Morozova S V, Savvateeva D M and Petrova E I 2015 *Nevrologicheskij zhurnal* **19(1)** 4 (In Russ.)
[6] Chernikova I V, Goncharova Z A, Hadzieva H I and Rabadanova E A 2015 *Kubanskij nauchnyj medicinskij vestnik* **3(152)** 134-9 (In Russ.)
[7] Kwon K, Lee H M, Lee S, Kang S H and Koh S 2016 *Journal of the Neurological Sciences* **361** 34-8
[8] Alekseeva N S, Illarioshkin S N, Ponomareva T A, Fedotova E Ju and Ivanova-Smolenskaja I A

2012 *Nevrologicheskij zhurnal* **17(1)** 10-4 (In Russ.)
[9] Voznesenskaya A E, Klyuchnikova M A, Rodionova E I and Voznesenskaya V V 2011 *Sensornye sistemy* **25(1)** 17-32 (In Russ.)
[10] Krismer F, Pinter B, Mueller C, Mahlknecht P, Nocker M, Reiter E, Djamshidian-Tehrani A, Boesch SM, Wenning GK, Scherfler C and Poewe W 2017 *Parkinsonism & related disorders* **35** 36-41
[11] Fullard M E, Morley J F and Duda J E 2017 *Neuroscience bulletin* **33(5)** 515-25
[12] Nielsen T, Jensen M B, Stenager E and Andersen A D 2018 *Danish medical journal* **65(5)** 1-10
[13] Vasechkin S V and Levin O S 2018 *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova. Specvypuski* **118(6)** 64-72 (In Russ.)
[14] Zhukova I A, Zhukova N G, Izhboldina O P, Nikitina M A and Alifirova V M 2015 *Zhurnal psikhiatrii i nevrolgii* **115(6-2)** 44-9 (in Russ.)
[15] Godoy M D, Voegels R L, Pinna F D, Imamura R and Farfel J M 2015 *International Archives of Otorhinolaryngology* **19** 176-9
[16] Hummel T B, Sekinger S R, Wolf E, Pauli G and Kobal A 1997 *Chemical Senses* **1** 39-52
[17] Fukunaga K 1972 *Introduction to statistical pattern recognition* (New York: London)
[18] Gorban A N, Kégl B, Wunsch D C and Zinovyev A Y 2008 *Principal manifolds for data visualization and dimension reduction* (Berlin: Springer) **58** 96-130
[19] Pokhabov D D, Tunik M E, Abramov V G, Tutsenko K O, Khoroshavina A A, Sadovsky M G and Pokhabov D V 2020 *Siberian Medical Review* **2** 58-66
[20] Pokhabov D V, Tunik M E, Abramov V G, Tutsenko K O, Khoroshavina A A, Sadovsky M G and Pokhabov D D 2019 *Neuroinformatics, its application and data analysis (*Krasnoyarsk) 87-95