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Correlation Analysis of Data of Tongue and Pulse in Patients With Disease Fatigue and Sub-health Fatigue

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Abstract

Fatigue is one of the most common subjective symptoms of abnormal health state, there is still no reliable and stable evaluation method to distinguish disease fatigue and non-disease fatigue. Studies have shown that tongue diagnosis and pulse diagnosis are the reflection of overall state of the body. This study aims to explore the distribution rules and correlation of data of tongue and pulse in population with disease fatigue and sub-health fatigue and provide a new method of clinical diagnosis of fatigue from the perspective of tongue diagnosis and pulse diagnosis. In this study, a total of 736 people were selected and divided into healthy controls (n = 250), sub-health fatigue group (n = 242), and disease fatigue group (n = 244). TFDA-1 tongue diagnosis instrument and PDA-1 pulse diagnosis instrument were used to collect tongue image and sphygmogram, simple correlation analysis and canonical correlation analysis were used to analyze the correlation of tongue and pulse data about the two groups of fatigue people. The study had shown that tongue and pulse data could provide a certain reference for the diagnosis of different types of fatigue, tongue and pulse data in disease fatigue and sub-health fatigue population had different distribution rules, and there was a simple correlation and canonical correlation in the disease fatigue population, the coefficient of canonical correlation was .649 (P <.05).

Keywords

fatigue, tongue data, pulse data, correlation analysis, health assessments

1. What do we already know about this topic?

Fatigue is an important message for health warnings, it is of great significance to distinguish disease fatigue from non-disease fatigue, due to the lack of objective diagnostic evidence of fatigue, there is still no reliable and stable evaluation method to distinguish disease fatigue and non-disease fatigue.

2. How does your research contribute to the field?

Based on the data of tongue and pulse, explored the diagnostic features of different styles of fatigue, it provided a methodological reference for the objective diagnosis of disease fatigue and non-disease fatigue.

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3. What are your research's implications toward theory, practice, or policy?

This is a relatively new work, by analyzing the correlation and diagnostic characteristics of tongue and pulse of 2 types of fatigue, it will open up new opportunities for future comprehensive health assessments.

Introduction

Fatigue is a subjective uncomfortable feeling of weakness, it is not only a physiological manifestation, but also a pathological result of disease states.[1] Fatigue can be divided into physical fatigue and mental fatigue. Different diseases can cause different degrees of fatigue. In some diseases, fatigue is more obvious and can be used as the first symptoms of clinical treatment.[2] Fatigue is closely related to people's physical and mental health. As a non-specific symptom, fatigue generally exists in people with sub-health and various diseases,[3-5] and it can affect people's quality of life to varying degrees.[4,6,7] Fatigue restricts people's daily activities, especially for elderly men and women and patients with chronic diseases or disabilities, and seriously affects people's living standards.[8] Clinically, when doctors face fatigue people, they cannot quickly and accurately determine whether they are in disease state. Whether it is disease fatigue or sub-health fatigue, early and timely intervention is of great significance. So, it is of great importance to find convenient and effective methods for fatigue differential diagnosis.

Tongue diagnosis and pulse diagnosis are comprehensive diagnosis methods based on overall state of the body. They are suitable for the comprehensive evaluation of the functional state of the body and have become an important objective basis of health state evaluation and syndrome diagnosis. In recent years, data-based researches and applications based on tongue diagnosis and pulse diagnosis have been launched, and breakthroughs have been made in quantification and standardization. The applications of modern tongue diagnosis and pulse diagnosis technology to fatigue research are also increasing day by day, providing a quantitative diagnosis basis for fatigue diagnosis in Traditional Chinese Medicine (TCM).[9,10] Xu JT et al.[11] established a chronic exercise fatigue model to detect the sphygmogram before and after fatigue, the results showed that the sphygmogram changes after chronic exercise fatigue were mainly characterized by the increased w/t (the ratio of the width of the main wave to the entire pulse cycle, it represents the duration of elevated aortic pressure), wide and large main wave, raised and moved forward of h_4 (dicrotic notch amplitude, it mainly reflects the peripheral vascular resistance and the function of aortic valve closure) in the descending isthmus. However, due to the multi-dimensional and subjective nature of fatigue, reasonable evaluation and precise treatment still have certain difficulties. The current evaluation of fatigue is mainly based on subjective scale evaluations, and there is a lack of effective objective evaluation methods. Therefore, using modern technology to further understand the mechanism of subjective fatigue will be helpful for doctors to develop more effective new methods of diagnosis and treatment, so as to better improve the quality of life of patients.[12] Therefore, the establishment of a new method of fatigue diagnosis and evaluation based on certain objective data is very valuable for the treatment and intervention of fatigue.

Our research team has long been engaged in research on informatization and intelligence of TCM diagnosis technology. From the perspective of modern science and biomedical engineering, we have independently researched and developed pulse diagnosis instrument and tongue diagnosis instrument, and preliminarily realized the data collection, analysis, and diagnosis of tongue and pulse data. Based on the objective data of tongue and pulse, we interpreted the rules of disease diagnosis, and established the relationship between tongue/pulse and health status, hypertension, diabetes, tumor and, other diseases.[13,14] The results obtained in our previous study also laid an important foundation for the establishment of fatigue diagnosis method based on tongue and pulse data. So, this study explored the differences of fatigue groups in different states from the perspective of correlation of tongue and pulse data, in order to provide new ideas and methods for the differential diagnosis of fatigue, especially fatigue caused by early disease. It mainly provided methodological support for the differential diagnosis of fatigue status from different dimensions.

Methods

Data Source and Sample

Participants in the Health Examination Center of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine were selected from January 2015 to December 2018. According to the diagnostic criteria of disease and sub-health, the subjects were divided into 3 groups: healthy controls (n = 250), sub-health fatigue group (n = 242), and disease fatigue group (n = 244), the diseases mainly include hypertension, diabetes, and hyperlipidemia.

Diagnostic Criteria

According to the diagnostic criteria of diabetes,[15] hypertension,[16] and hyperlipidemia,[17] diagnosis can be made if one or more of the following conditions were met: (1) Fasting plasma glucose ≥6.1 mmol/L and/or 2h plasma glucose after meal ≥ 7.8/L. (2) Blood pressure ≥130/85 mmHg. (3) Triglyceride ≥1.70 mmol/L. (4) High-density lipoprotein cholesterol <1.04 mmol/L.

The Health Status Assessment Questionnaire Scale (H20)[18] and the Information Record of Four Diagnoses of TCM[19] (No.:2016Z11L025702) were used to record the symptoms.

(1) Disease fatigue population: be diagnosed with diseases and had fatigue symptom. (2) Sub-health fatigue population: Western medicine physical examination indices had no obvious positive items, H20 scores were 60–79 points and had a fatigue symptom. (3) Healthy controls: Western medicine physical examination indices had no obvious positive items, H20 scores were 80–100 points and didn't have a fatigue symptom.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Meet the diagnostic criteria of disease or sub-health. (2) Complete information of TCM and Western medicine, know and sign the informed consent. (3) Between 18 and 90 years old.

Exclusion criteria: (1) Those who did not meet the inclusion criteria. (2) Pregnant or lactating women. (3) Patients with mental illness or poor compliance.

Collection of Clinical Tongue and Pulse Data

Tongue and pulse data were collected using the Tongue and Face Diagnosis Analysis-1(TFDA-1) instrument and Pulse Diagnosis Analysis-1(PDA-1) instrument developed by the national key research and development plan. The TFDA-1 digital tongue and surface diagnosis instrument and its corresponding analysis system were shown in Figures 1 and 2, and the PDA-1 digital pulse diagnosis instrument and its corresponding sphygmogram were shown in Figures 3 and 4. Tongue diagnosis and pulse diagnosis data collection was completed by clinical graduate students who had received standardized training to ensure the standardization and accuracy of the data.

The color parameters of tongue image in Figure 2 come from four color spaces: RGB, HSI, Lab, and YCrCb.[20-22] They are R (red), G (green), and B (blue), H (hue), S (saturation), I (brightness), L (lightness), a (red-green axis), b (yellow-blue axis), Y (brightness), Cr (the difference between the red part of the RGB input signal and the brightness value of the RGB signal), Cb (the difference between the blue part input signal and the brightness value of RGB signal). Texture indices include Con (Contrast), ASM (Angular Second Moment), ENT (Entropy), MEAN, tongue coating indices includes perAll, perPart. perAll represents the ratio of the coated tongue area to the total tongue area, perPart represents the ratio of the coated tongue area to the non-coated tongue area. Prefix "TB-" indicates tongue body, and "TC-" indicates tongue coating. "H" with angle range of $[0,2\pi]$ represents the hue. Angle 0 is for pure red, Angle $2\pi/3$ is for pure green, and Angle $4\pi/3$ is for pure blue. In this study, in order to better reflect the continuity of the trend, so as to find the data rules and real differences, this study redefined the value of TB-H after it was rotated 180° according to the rule.

In Figure 3, h_1–h_5 mainly represent the amplitude height. h_1 is the main wave amplitude, h_3 is heavy wave front wave amplitude, h_3/h_1 is the ratio of heavy wave front wave amplitude to the amplitude of the main wave, h_4 is the dicrotic notch amplitude, h_4/h_1 is the ratio of the dicrotic notch amplitude to the amplitude of the main wave, h_5 is the gravity wave amplitude, and h_5/h_1 is the ratio of gravity wave amplitude to the amplitude to the amplitude of the main wave. t represents a complete pulse cycle, t_1 is the time value from the

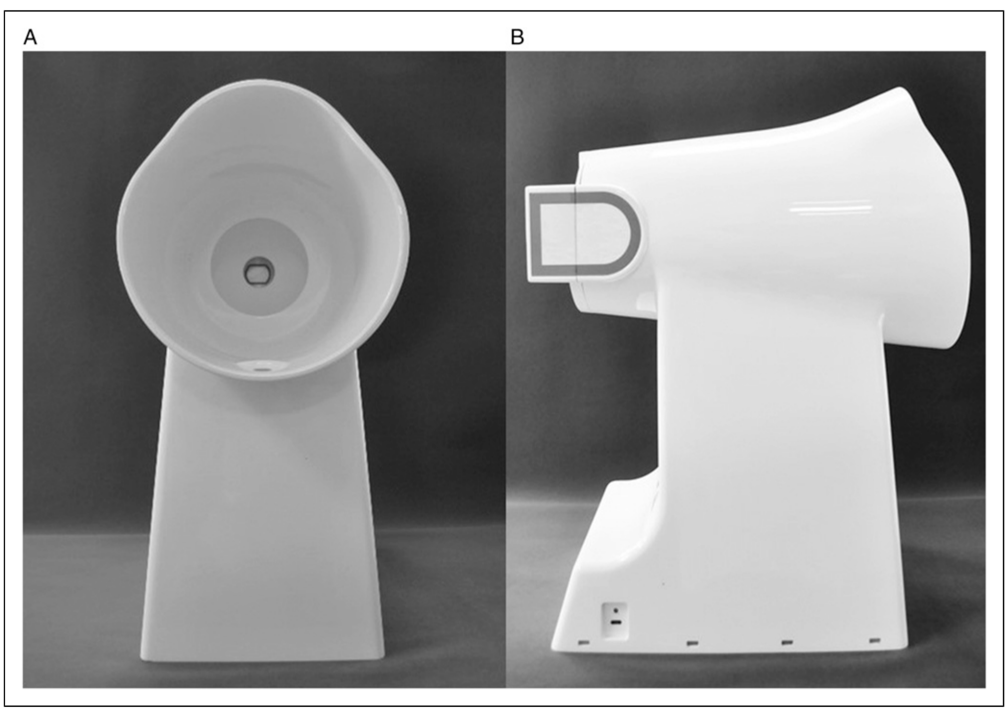

Figure 1. TFDA-1 digital tongue and face diagnosis instrument. (A) Front view; (B) Profile view.

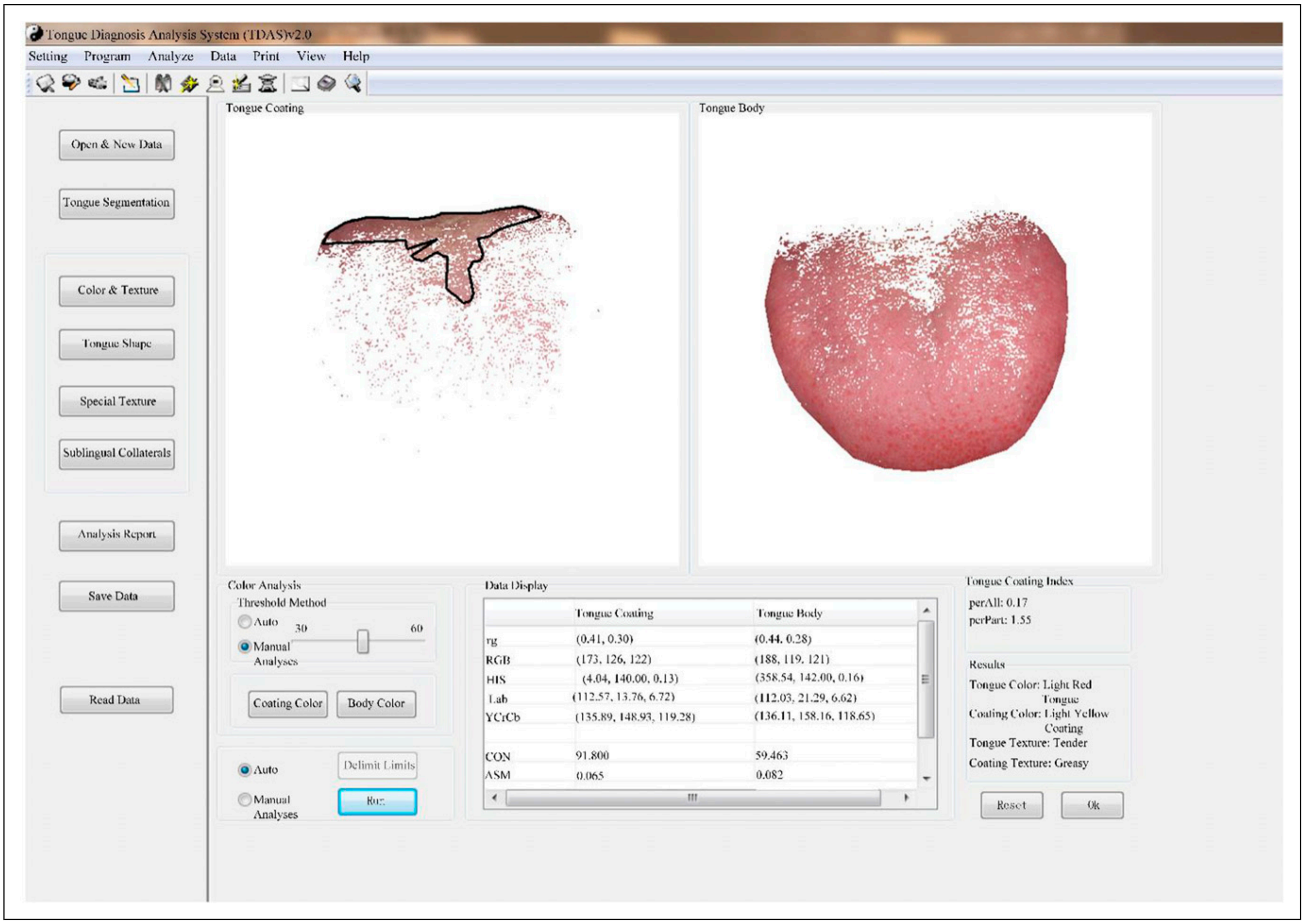

Figure 2. Tongue image analysis system.

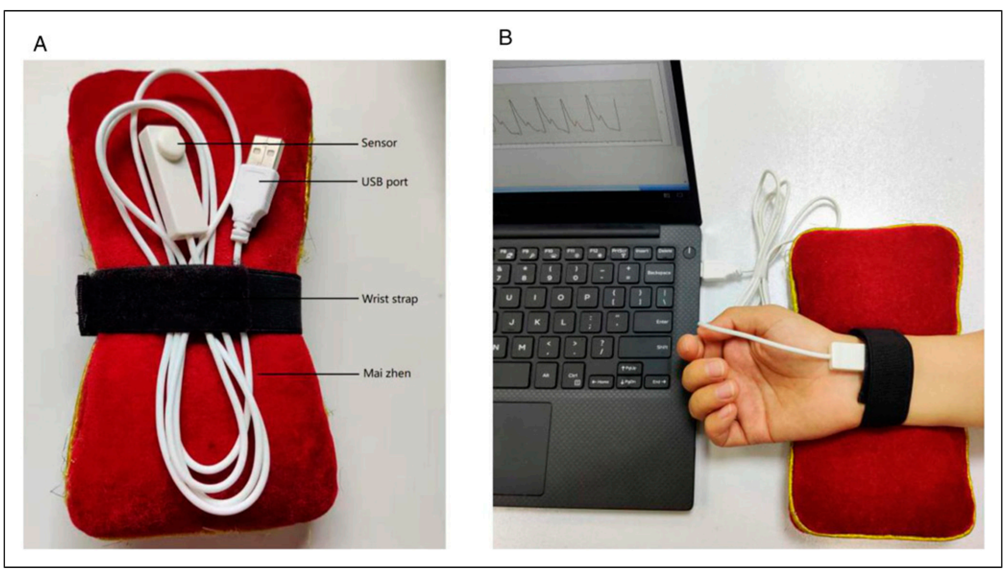

Figure 3. PDA-1 digital pulse diagnosis instrument.

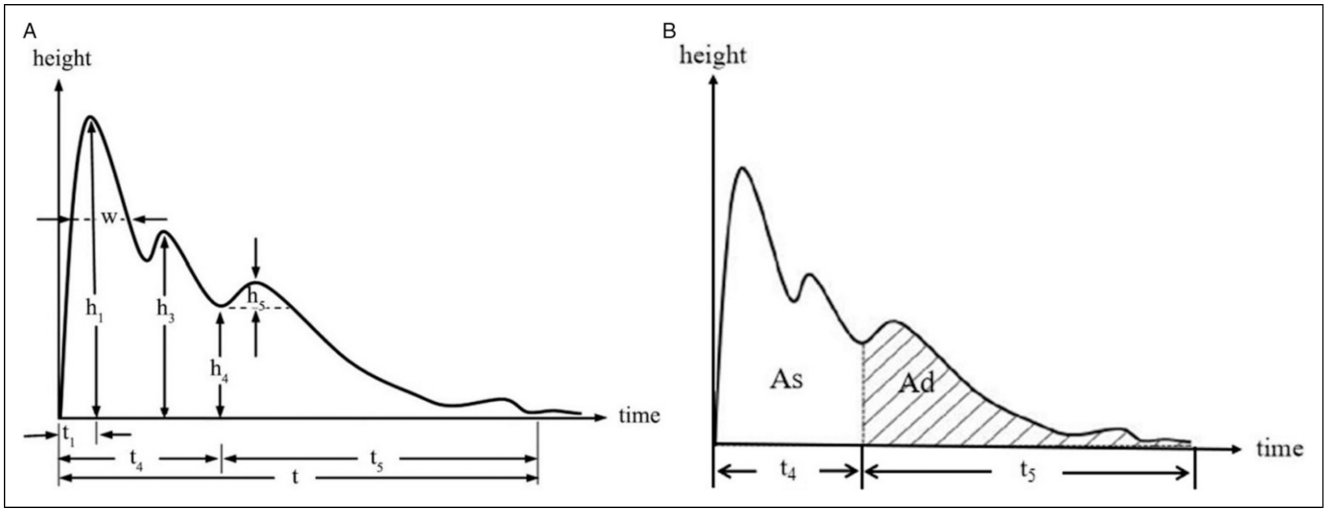

Figure 4. Sphygmogram and its parameters.

start point to the crest point of the main wave on the sphygmogram, t_4 is the time value from the start point to the dicrotic notch on the sphygmogram, t_5 is the time value from the dicrotic notch to the end point on the sphygmogram. w_1 is the width at 1/3 of the main wave, w_2 is the width at 1/5 of the main wave, As is the systolic area, Ad is the diastolic area.

Tongue image acquisition methods of TFDA-1 digital tongue diagnosis instrument were as follows:[23] (1) Set shooting parameters, and conduct alcohol disinfection on the instrument. (2) Instruct the subjects to place their chin on the mandibular rest of the tongue diagnosis instrument, open their mouth, naturally relax the tongue body, flatten the tongue body with the tip of the tongue down, after the tongue body is stable, touch the center of the tongue surface in the tongue diagnosis instrument camera quickly and lightly to complete the collection. (3) Check the captured images, and require the tongue surface is complete and not tense, no fog cover, no light leakage, no overexposure or underexposure. Those who do not meet the above requirements need to re-shoot.

Sphygmogram acquisition methods of the PDA-1 digital pulse diagnosis instrument were as follows:[24] (1) The subjects take a seated position with the forearm relaxed, and the elbow is at 120°. Place the wrist on the pulse pillow with the palm facing up, and keep breathing steady. (2) Place the probe in the most obvious pulse fluctuation of the left radial artery and fix it with a band. (3) Adjust the position of the probe and the tightness of the band until the pulse amplitude is maximum and the sphygmogram is stable and collected for 30 seconds to obtain the best sphygmogram.

Statistical Analysis

SPSS 25.0 software was used for statistical analysis. Measurement data that obey the normal distribution was represented by "$\bar{X} \pm S$", those that did not obey were represented by quartiles. Comparisons between groups were subjected to analysis of variance for those who obeyed normality and homogeneity of variance, while nonparametric rank sum test was performed for those who did not obey.

Using Canonical Correlation Analysis (CCA) to do the correlation analysis of tongue and pulse data, CCA was a multivariate statistical analysis method to study the correlation between two groups of variables. In this study, tongue parameters were set as set U and pulse parameters as set V, SPSS25.0 statistical software was used for canonical correlation analysis, and using GraphPad Prism 8.0 do correlation heat maps. All tests were two-tailed tests. $P < .05$ indicated that the difference was statistically significant.

Results

Baseline Characteristics

Baseline Characteristics of the three groups were shown in Table 1. It could be seen from the statistical results that the age and Body Mass Index (BMI) of the disease fatigue group were significantly different from those of the sub-health fatigue group and the healthy controls ($P < .01$), while there were no significant differences in age and BMI between the sub-health fatigue group and the healthy controls ($P > .05$).

Statistical Analysis of Tongue Parameters

Statistical results of tongue parameters in the three groups were shown in Table 2. Results of tongue image parameters showed that there were more significant differences between the disease fatigue group and the healthy controls. TB-R, TB-H, TB-Cb, TB-b, TC-b, TC-H, and TC-Cb had significant differences between the sub-health fatigue group and the healthy controls ($P < .05$, $P < .01$); TB-R, TB-H, TB-Cb, TB-b, TC-b, TC-H, TC-Cb, TB-B, TB-I, TB-S, TB-Con, TB-ASM,

Table 1. Baseline Characteristics of the 3 Groups.

Groups	Number	Sex [N (%)]		Age (year)			
		Male	Female	Minimum	Maximum	Average ($\bar{X} \pm S$)	BMI ($\bar{X} \pm S$)
Healthy controls	250	161 (64.4)	89 (35.6)	19	62	32.62 ± 8.98	22.83 ± 3.41
Sub-health fatigue group	242	146 (60.3)	96 (39.7)	20	74	33.69 ± 9.00	22.76 ± 3.56
Disease fatigue group	244	183 (75.0)	61 (25.0)	26	79	51.18 ± 12.53##**	25.92 ± 3.35##**

#vs. Healthy controls, $P < .05$, ##vs. Healthy controls, $P<.01$.
*vs. Sub-health fatigue group, $P<.05$, **vs. Sub-health fatigue group, $P<.01$.

Table 2. Statistical Analysis of Tongue Parameters in the 3 Groups [Mean (Standard Deviation), Median (P25, P75)].

Domain	Parameters		Healthy controls (N = 250)	Sub-health fatigue group (N = 242)	Disease fatigue group (N = 244)
TB	RGB	TB-R	152.62 (18.37)	152.62 (18.37)#	155.12 (20.71)
		TB-G	98.12 (15.32)	98.12 (15.32)	101.14 (18.31)
		TB-B	99.50 (90.75,112.00)	153.00 (138.75,166.00)	115.50 (100.00,125.00)##**
	Lab	TB-L	103.75 (5.68)	103.75 (5.68)	104.84 (6.53)
		TB-a	19.37 (17.57,21.70)	20.47 (18.10,22.68)	21.12 (18.69,23.47)##
		TB-b	6.41 (5.03,7.70)	5.04 (.55,6.93)##	1.71 (-5.33,5.29)##**
	HIS	TB-H	179.13 (177.00,181.66)	176.63 (167.87,180.00)##	170.80 (153.12,176.89)##**
		TB-I	117.00 (107.00,129.00)	118.00 (106.00,130.00)	120.00 (112.00,135.00)##*
		TB-S	.17 (.15,0.19)	.18 (.15,0.20)	.19 (.16,0.21)##
	YCrCb	TB-Y	114.98 (13.50)	114.98 (13.50)	117.98 (15.76)
		TB-Cr	151.61 (149.13,153.91)	151.31 (148.38,153.87)	150.66 (147.88,153.85)
		TB-Cb	120.28 (118.98,121.48)	121.31 (119.83,125.29)##	124.01 (120.70,130.69)##**
	Texture index	TB-Con	71.73 (50.19,103.64)	68.00 (40.93,98.95)	58.53 (39.59,86.81)##
		TB-ASM	.08 (.07,0.09)	.08 (.07,0.10)	.09 (.07,0.10)##
		TB-ENT	1.21 (1.13,1.29)	1.20 (1.08,1.28)	1.16 (1.08,1.26)##
		TB-MEAN	.03 (.02,0.03)	.02 (.02,0.03)	.02 (.02,0.03)##
TC	RGB	TC-R	149.00 (139.00,161.25)	149.00 (137.00,163.00)	151.00 (139.25,165.75)
		TC-G	114.00 (103.00,125.00)	114.00 (103.00,125.00)	116.00 (105.00,129.75)
		TC-B	116.00 (102.00,127.25)	118.00 (105.00,134.25)	127.50 (112.00,147.00)##**
	Lab	TC-L	107.91 (103.96,111.42)	107.93 (104.09,112.05)	109.14 (105.15,113.13)#
		TC-a	12.76 (2.75)	12.76 (2.75)	12.71 (3.03)
		TC-b	4.84 (3.77,6.20)	3.26 (-1.05,5.10)##	.88 (−6.59,4.08)##**
	HIS	TC-H	181.80 (180.00,184.84)	177.49 (161.89,182.42)##	169.76 (132.73,178.59)##**
		TC-I	126.00 (115.00,137.00)	127.00 (115.00,140.00)	131.00 (119.00,146.00)##*
		TC-S	.12 (.03)	.12 (.03)	.12 (.03)
	YCrCb	TC-Y	122.89 (113.53,132.11)	122.94 (113.80,133.72)	125.92 (116.58,137.03)#
		TC-Cr	143.66 (141.08,146.02)	143.23 (140.63,145.77)	142.44 (138.66,145.91)##
		TC-Cb	121.78 (120.71,123.11)	123.24 (121.63,127.73)##	125.61 (122.51,133.18)##**
	Area index	perAll	.47 (.40,0.60)	.52 (.41,0.76)	.62 (.43,0.90)##*
		perPart	1.14 (1.04,1.26)	1.09 (1.03,1.22)	1.05 (1.02,1.18)##*
	Texture index	TC-Con	84.21 (62.39,118.75)	88.45 (58.84,125.37)	88.45 (61.33,122.12)
		TC-ASM	.07 (.06,0.08)	.07 (.06,0.08)	.07 (.06,0.08)
		TC-ENT	1.25 (1.18,1.33)	1.26 (1.17,1.34)	1.26 (1.18,1.34)
		TC-MEAN	.03 (.02,0.03)	.03 (.02,0.03)	.03 (.02,0.03)

#vs. Healthy controls, $P < .05$, ##vs. Healthy controls, $P < .01$.
*vs. Sub-health fatigue group, $P < .05$, **vs. Sub-health fatigue group, $P < .01$.

TB-ENT, TB-MEAN, TC-B, TC-L, TC-Y, TC-Cr, perAll, and perPart had significant differences between the disease fatigue group and the healthy controls ($P < .05$, $P < .01$); TB-B, TB-b, TB-H, TB-I, TB-Cb, TC-B, TC-b, TC-H, TC-I, TC-Cb, perAll, and perPart showed statistically significant differences between sub-health fatigue group and disease fatigue group ($P < .05$, $P < .01$); TB-b, TB-H, TC-b, TC-H, and perPart in the three groups had the following order: disease fatigue group < sub-health fatigue group < healthy controls. TB-I, TB-Cb, TC-B, TC-I, TC-Cb, and perAll had the following order: healthy controls < sub-health fatigue group < disease fatigue group.

Table 3. Statistical Analysis of Pulse Parameters in the 3 Groups [Mean (Standard Deviation), Median (P25, P75)].

Parameters	Healthy controls (N = 250)	Sub-health fatigue group (N = 242)	Disease fatigue group (N = 244)
t_1 (s)	.13 (.12,0.14)	.13 (.12,0.14)	.14 (.13,0.15)$^{\#\#**}$
t_2 (s)	.22 (.21,0.23)	.22 (.21,0.24)	.23 (.22,0.26)$^{\#\#**}$
t_3 (s)	.26 (.25,0.27)	.26 (.25,0.27)	.27 (.25,0.29)$^{\#\#**}$
t_4 (s)	.34 (.33,0.36)	.34 (.33,0.36)	.36 (.34,0.38)$^{\#\#**}$
t_5 (s)	.41 (.39,0.42)	.40 (.39,0.42)	.41 (.39,0.43)
h_1 (mv)	113.47 (96.27,135.47)	110.79 (90.78,132.93)	115.17 (88.77,146.18)
h_2 (mv)	80.59 (62.17,100.60)	76.80 (61.22,97.16)	77.15 (56.36,114.12)
h_3 (mv)	72.90 (56.40,90.74)	70.12 (56.00,87.64)	71.40 (52.46,104.51)
h_4 (mv)	43.92 (35.09,53.81)	41.99 (33.05,51.75)	41.67 (30.19,56.70)
h_5 (mv)	3.50 (1.13,6.71)	3.24 (.65,6.09)	.87 (-.53,3.16)$^{\#\#**}$
w_1 (s)	.17 (.13,0.19)	.17 (.14,0.19)	.18 (.15,0.20)$^{\#\#*}$
w_2 (s)	.11 (.09,0.14)	.11 (.09,0.14)	.13 (.11,0.16)$^{\#\#**}$
W_1/t	.20 (.17,0.23)	.20 (.18,0.23)	.22 (.19,0.24)$^{\#\#*}$
W_2/t	.13 (.11,0.16)	.14 (.11,0.17)	.16 (.13,0.18)$^{\#\#**}$
h_1/t_1	878.98 (744.81,1063.52)	862.66 (695.92,1044.81)	837.90 (642.70,1047.82)
h_3/h_1	.64 (.56,0.74)	.64 (.56,0.73)	.67 (.57,0.77)
h_4/h_1	.38 (.33,0.44)	.38 (.33,0.44)	.37 (.31,0.42)
As (mv·s)	.20 (.19,0.23)	.21 (.19,0.23)	.22 (.20,0.24)$^{\#\#**}$
Ad (mv·s)	.11 (.09,0.13)	.11 (.09,0.13)	.09 (.07,0.11)$^{\#\#**}$
t (s)	.83 (.77,0.90)	.82 (.77,0.90)	.82 (.75,0.92)

$^{\#}$vs. Healthy controls, $P < .05$, $^{\#\#}$vs. Healthy controls, $P < .01$.
*vs. Sub-health fatigue group, $P < .05$, **vs. Sub-health fatigue group, $P < .01$.

Statistical Analysis of Pulse Parameters

Statistical results of pulse parameters in the three groups were shown in Table 3. Results of sphygmogram parameters showed that there were no significant differences between the sub-health fatigue group and the healthy controls. There were statistically significant differences in t_1, t_2, t_3, t_4, h_5, w_1, w_2, w_1/t, w_2/t, As, and Ad between the disease fatigue group and the healthy controls, and between the sub-health fatigue group and the disease fatigue group ($P < .05$, $P < .01$). Among them, the distribution trends of t_1, t_2, t_3, t_4, w_1, w_2, w_1/t, w_2/t, and As in the 3 groups were: healthy controls <sub-health fatigue group <disease fatigue group ($P < .05$, $P < .01$), the distribution trend of h_5 and Ad in the three groups was: disease fatigue group <sub-health fatigue group <healthy controls.

Simple Correlation Analysis of Tongue and Pulse Parameters

Using GraphPad Prism 8 software to select the tongue and pulse parameters with statistically significant differences among the three groups for further correlation analysis, the heat maps of the tongue and pulse parameters of the three groups were shown in Figure 5.

The correlation matrix of tongue and pulse parameters in the sub-health fatigue group was not statistically significant. The tongue and pulse parameters correlation matrix of the healthy controls and the disease fatigue group were shown in Tables 4 and 5, and the correlation heat maps of tongue and pulse parameters were shown in Figures 6 and 7, label each cell with their correlation coefficients.

There was a certain correlation between pulse parameters t_1 and tongue texture parameters TB-Con, TB-ASM, TB-ENT, and TB-MEAN in the healthy controls (correlation coefficients were −.14, .14, −.14, −.14, $P < .05$). In the disease fatigue group, more tongue and pulse parameters were correlated, the correlation coefficients of w_2/t and perAll, TC-Cr, TB-b, TB-Cb were .25, −.23, −.18, 018 (P<.01), the correlation coefficients of w_1/t and perAll and w_1/t and TC-Cr were .19 and −.19, respectively ($P < .05$), the correlation coefficients of t_1 and perAll and t_1 and perPart were .19 and −.19 ($P < .05$), and the correlation coefficient of h_5 and perAll was −.18 ($P < .05$).

Canonical Correlation Analysis of Tongue and Pulse Parameters

Results of Correlation Coefficient of Canonical Variables. Define 34 tongue parameters as set U and 20 pulse parameters as set V for CCA. The results showed that the tongue and pulse parameters of the healthy controls and the sub-health fatigue group had no significant canonical correlation. While the disease fatigue population obtained 20 pairs of tongue and pulse canonical correlation variables.

The canonical correlation coefficients were calculated, respectively, and Bartlett$\chi 2$ hypothesis test was performed.

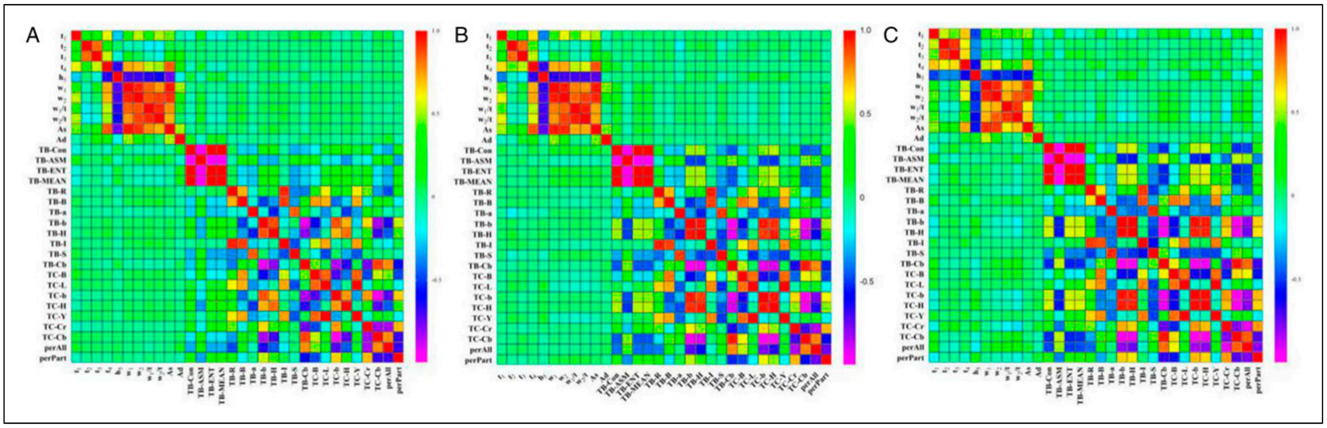

Figure 5. Correlation heat map of tongue and pulse parameters in the three groups of population. (A): Correlation heat map of tongue and pulse parameters in the healthy controls; (B): Correlation heat map of tongue and pulse parameters in the sub-health fatigue group; (C): Correlation heat map of tongue and pulse parameters in the disease fatigue group.

Table 4. Simple Correlation Analysis of Tongue and Pulse Parameters in the Healthy Controls.

Parameters	t_1
TB-Con	−.143*
TB-ASM	.139*
TB-ENT	−.144*
TB-MEAN	−.144*

Canonical Loadings Coefficient

The canonical loadings coefficient is also called the structural correlation coefficient, which refers to the simple correlation coefficient between a canonical variable and all variables in this group, and the cross loadings coefficient refers to the simple correlation coefficient between a correlation variable and all the variables in another set of variables.

Table 5. Simple Correlation Analysis of Tongue and Pulse Parameters in the Disease Fatigue Group.

Parameters	t_1	t_3	h_5	w_2	w_1/t	w_2/t
TB-Con	−.136*	.096	.062	−.027	.009	−.079
TB-ASM	.135*	−.118	−.052	.037	.010	.098
TB-ENT	−.134*	.106	.061	−.032	.001	−.090
TB-MEAN	−.134*	.105	.056	−.030	.003	−.086
TB-b	−.159*	.071	.138*	−.106	−.112	−.175**
TB-H	−.141*	.056	.118	−.082	−.075	−.143*
TB-Cb	.160*	−.077	−.130*	.105	.116	.179**
TC-B	.136*	−.012	−.104	.076	.100	.127*
TC-b	−.134*	.068	.136*	−.085	−.106	−.158*
TC-H	−.125*	.054	.143*	−.068	−.068	−.127*
TC-Cr	−.153*	.135☆	.126	−.104	−.194*	−.231**
TC-Cb	.131*	−.066	−.128*	.077	.102	.153*
perAll	.186**	−.113	−.184**	.153*	.186*	.247**
perPart	−.190**	−.037	.148*	−.071	−.100	−.141*

*, $P < .05$, **, $P < .01$.

The first pair of canonical correlation coefficients was statistically significant ($P < .01$). And the canonical correlation result was shown in Table 6. Among them, the first pair of canonical correlation variables was real, the first pair of canonical correlation coefficient was .627, the eigenvalue was .649, F = 1.180, $P < .001$.

The results of the canonical loadings and cross loadings of tongue parameters in the disease fatigue group were shown as Table 7. In the first canonical variable U1, TC-Cr, TC-Cb, TB-b, perPart, TB-Cb, TC-b, and TC-H had higher canonical loadings, which were .353, −.349, .347, .344, −.344, .34, .332, respectively. The canonical cross loadings on the other side were .222,

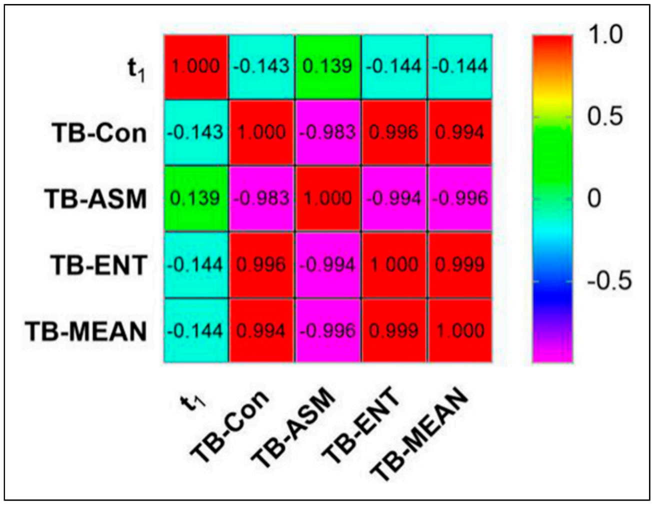

Figure 6. Correlation heat map of tongue and pulse parameters in the healthy controls.

−.219, .218, .216, −.216, .213, .208, and the cross loadings on the other side were .222, −.219, .218, .216, −.216, .213, .208, respectively. The rest of the tongue parameters were smaller in both of its own canonical loadings and the cross loadings.

The results of the canonical loadings and cross loadings of pulse parameters in the disease fatigue group were shown in Table 8. In the first canonical variable V1, the canonical loadings and cross loadings of t_5, w_2/t and t_4 were larger, the canonical loadings were .387, −.271, and .268, respectively, and the cross loadings were .243, −.17, and .168, respectively.

Canonical Correlation Structure Diagram

The structure diagram was used to show the correlation coefficient matrix between the original variables and the canonical correlation variables.[25] Select representative tongue and pulse parameters, the first canonical correlation variable structure diagram was shown in Figure 8. TC-Cr, TC-Cb, TB-b, TB-Cb, perPart, TC-b, and TC-H could better reflect the first canonical correlation variable U1 (canonical correlation coefficients were .353, −.349, .347, −.344, .344, .340, .332, $P<.05$), TC-Cr, TB-b, perPart, TC-b, TC-H were positively correlated with U1, TC-Cb, TB-Cb were negatively correlated with U1. t_5, w_2/t and t_4 could better reflect the first canonical correlation variable V1 of pulse parameters (canonical correlation coefficients were .387, −.271, .268, $P < .05$), t_5, t_4 were positively correlated with V1, while w_2/t was negatively correlated with V1.

Discussions

Analysis of Tongue and Pulse Parameters in Sub-health Fatigue and Disease Fatigue Population

The upstream of sub-health is connected with health, and the downstream is crossed with disease, which is the turning point of human health. Fatigue is the main factor of sub-health, and should be treated in time, through the intervention of high-risk pathogenic factors, to prevent it from developing into a variety of diseases. Although people are very interested in fatigue, people know very little about fatigue, one of the reasons for this dilemma is the lack of effective experimental models of fatigue.[26] Currently, it is believed that the pathogenesis of fatigue is mainly related to dopamine,[27] hypothalamic-pituitary-thyroid axis disorders,[28] compensatory effect generated by negative feedback inhibition,[29] and activated immune inflammatory pathway.[30] Studies have shown that chronic fatigue syndrome mainly affects women,[31] but during muscle contractions of similar intensity, women are less prone to fatigue than men.[32] At present, many countries have proposed treatment recommendations, studies have shown that sleep disorders, depression, and fatigue seem to be related to each other, and new insights into the regulation of sleep balance may provide new clues for understanding and treating fatigue.[33] Fatigue has a great exploration space in diagnosis, treatment, and prognosis nursing.[34]

As our research samples were from health examination centers, and the data sampling reflected the real clinical gender distribution, that was, the total number of men participating in the physical examination was higher than that of women. The possible reason was that the number of male workers was significantly higher than that of female workers in the area where the hospital was located. Hypertension, diabetes, and hyperlipidemia are the most common diseases among those who underwent physical examination. Therefore, the above 3 groups of people were selected as the subjects of the disease fatigue group in this study. Age is indeed a factor that should be considered, but this study took age as an objective basic state, on this basis, the difference of tongue and pulse data was considered and analyzed, and further observed the difference of the correlation between tongue and pulse in each group of healthy controls, sub-health fatigue group, and disease fatigue group. In this study, the performance of TB-I, TB-Cb, TC-B, TC-I, TC-Cb, and perAll in the three groups of people had the following order: healthy controls < sub-health fatigue group < disease fatigue group. TB-Cb, TC-Cb, and TC-B gradually increased in the three groups of people. Cb reflects the difference between the blue part of RGB input signal and the brightness value. The higher the B value, the appearance of the tongue will appear blue or purple, indicating that the tongue of disease fatigue people was blue or purple; b is the yellow-blue axis, and the higher the b value, the more yellow of the tongue coating. The smaller the b value, the more the blue component of the tongue image, and the more blue-purple of the tongue body. In this study, TB-b, TB-H, TC-b, TC-H, and perPart in the three groups had the following order: disease fatigue group <sub-health fatigue group <healthy controls; TC-b and TB-b in the three groups, both of them showed a downward trend, indicating that the tongue body of disease fatigue people was slightly blue-purple. I and perAll gradually increased and

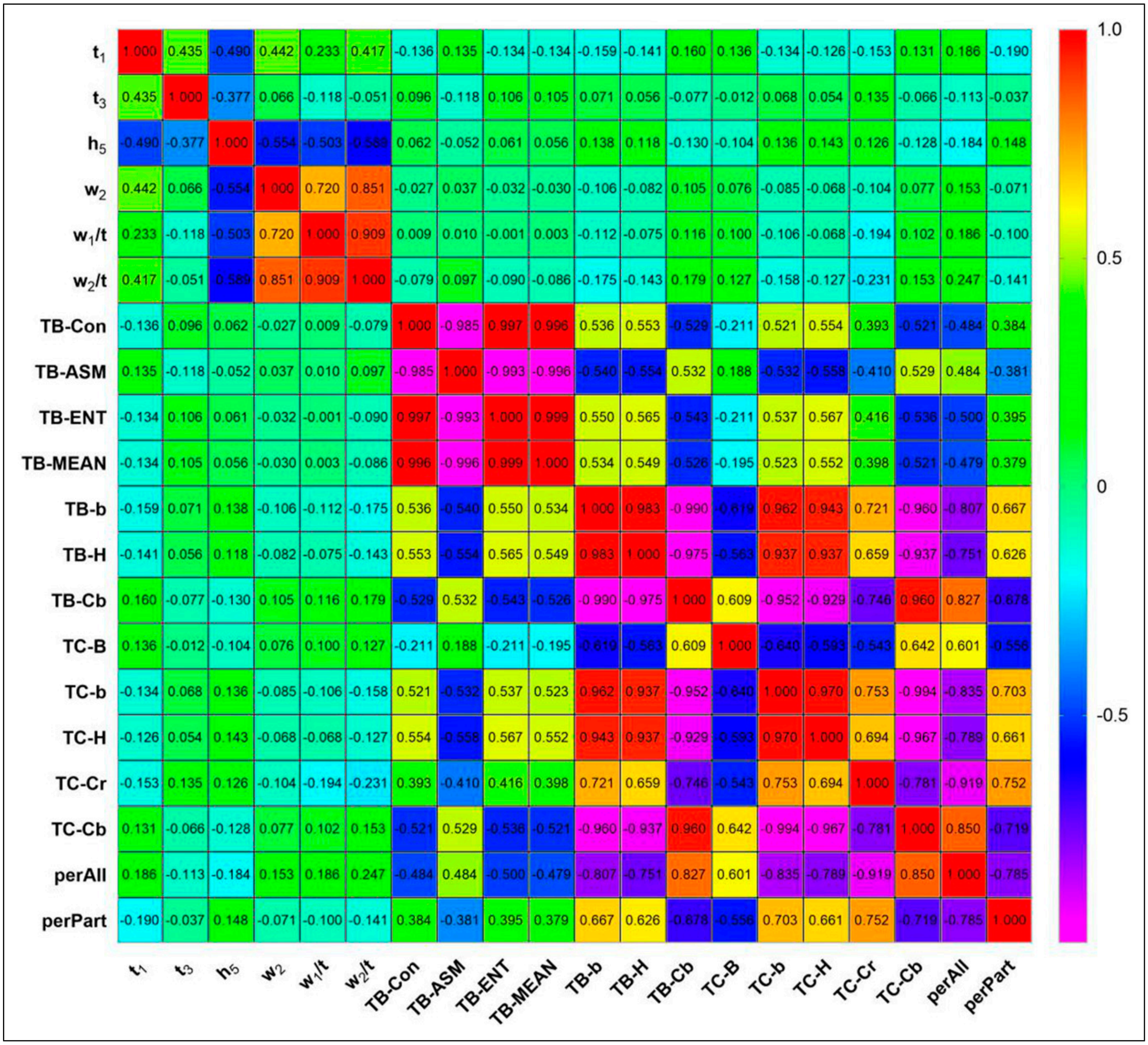

Figure 7. Correlation heat map of tongue and pulse parameters in the disease fatigue group.

perPart gradually reduced in the three groups of people, I value represents the brightness, the larger the I value, the closer to white, and the tongue tends to be pale. perAll is more valuable in the diagnosis of thick tongue coating, the larger the value, the thicker the tongue coating, and perPart is more valuable in the diagnosis of thin tongue coating, the larger the value, the thinner the tongue coating. Therefore, the tongue coating of people with disease fatigue was white and thick or greasy, and the tongue coating of healthy and sub-health people was thin. The t_1 value mainly represents the systolic period of the left ventricle. The larger the value, the longer the ventricular contraction time, the worsening of myocardial contractility or the increase of intraventricular pressure; The values of w1 and w_2 are the time for maintaining a high level of intraarterial pressure, and the larger the value explains poor elasticity of blood vessels and arteries, the larger the value, the poorer the vascular and arterial elasticity. The increase of w_1/t and w_2/t indicates poor vascular and arterial elasticity, or increased peripheral resistance of blood vessels. When the arterial elasticity is poor, the dicrotic wave appears early, close to or coincides with the main wave, when it is close to or coincides with the main wave, or when the peripheral resistance increases, h_3 increases, and a wide main wave will appear. h_5 represents the amplitude of the dicrotic wave, which mainly reflects the elasticity of the aorta and the function of the aortic valve. As represents the systolic area, which is related to cardiac output. Ad represents the diastolic area. The results of the study showed that the distribution trends of t_1, t_2, t_3, t_4, w_1,

Table 6. Canonical Correlation of Tongue and Pulse Parameters in the Disease Fatigue Group.

Canonical variable	Correlation	Eigenvalue	Wilks Statistic	F	P
1	.627	.649	.025	1.180	.002
2	.612	.600	.042	1.098	.061
3	.575	.493	.067	1.011	.424
4	.553	.441	.100	.936	.831
5	.541	.414	.144	.861	.982
6	.499	.332	.203	.776	1.000
7	.465	.276	.271	.703	1.000
8	.427	.223	.345	.636	1.000
9	.387	.176	.422	.579	1.000
10	.343	.133	.496	.533	1.000
11	.328	.121	.563	.501	1.000
12	.319	.113	.631	.466	1.000
13	.286	.089	.702	.420	1.000
14	.255	.069	.765	.381	1.000
15	.233	.057	.818	.35	1.000
16	.216	.049	.865	.320	1.000
17	.186	.036	.907	.284	1.000
18	.183	.035	.940	.256	1.000
19	.130	.017	.972	.186	1.000
20	.107	.011	.989	.160	1.000

Table 7. Loadings Coefficient of Tongue Parameters in the Disease Fatigue Group.

Parameters	Canonical Loadings	Cross Loadings	Parameters	Canonical Loadings	Cross Loadings
perAll	−.271	−.17	TB-I	.082	.051
perPart	.344	.216	TB-S	−.279	−.175
TB-Con	−.054	−.034	TC-H	.332	.208
TC-Con	−.099	−.062	TC-I	−.101	−.063
TB-ASM	−.073	−.046	TC-S	.055	.034
TB-ENT	.037	.023	TB-L	.137	.086
TB-MEAN	−.002	−.001	TB-a	−.22	−.138
TC-ASM	.088	.055	TB-b	.347	.218
TC-ENT	−.087	−.055	TC-L	−.082	−.051
TC-MEAN	−.076	−.048	TC-a	.187	.117
TB-B	−.073	−.046	TC-b	.34	.213
TB-R	.146	.092	TB-Y	.131	.082
TB-G	.155	.097	TB-Cr	.084	.053
TC-R	.065	.041	TB-Cb	−.344	−.216
TC-G	−.092	−.057	TC-Y	−.067	−.042
TC-B	−.227	−.142	TC-Cr	.353	.222
TB-H	.222	.14	TC-Cb	−.349	−.219

w_2, w_1/t, w_2/t, and As in the three groups of people had the following order: healthy controls <sub-health fatigue group <disease fatigue group ($P<.05$, $P<.01$), the distribution trend of h_5 and Ad in the three groups of people had the following order: disease fatigue group <sub-health fatigue group <healthy controls, indicating that disease fatigue people had poorer arterial elasticity than sub-health fatigue and healthy controls, or blood vessels peripheral resistance increases, and the pulse of disease fatigue people was wiry.

Correlation Analysis of Tongue and Pulse Parameters in Sub-health Fatigue and Disease Fatigue Population

Due to the large number of tongue and pulse parameters, the study did not completely show all tongue and pulse parameters, but only the parameters with statistical differences. Since there was no statistical difference in the correlation of tongue and pulse parameters in the sub-health fatigue group, the study did not show the relevant heat map. Tongue and

Table 8. Loadings Coefficient of Pulse Parameters in the Disease Fatigue Group.

Parameters	Canonical Loadings	Cross Loadings	Parameters	Canonical Loadings	Cross Loadings
t_1	−.085	−.053	w_1	−.111	−.07
t_2	.202	.126	w_2	−.176	−.11
t_3	.228	.143	w_1/t	−.213	−.134
t_4	.268	.168	w_2/t	−.271	−.17
t_5	.387	.243	h_1/t_1	.01	.006
h_1	.022	.014	h_3/h_1	−.147	−.092
h_2	−.117	−.074	h_4/h_1	.114	.071
h_3	−.098	−.061	As	.095	.06
h_4	.053	.033	Ad	−.037	−.023
h_5	−.209	−.131	t	.037	.023

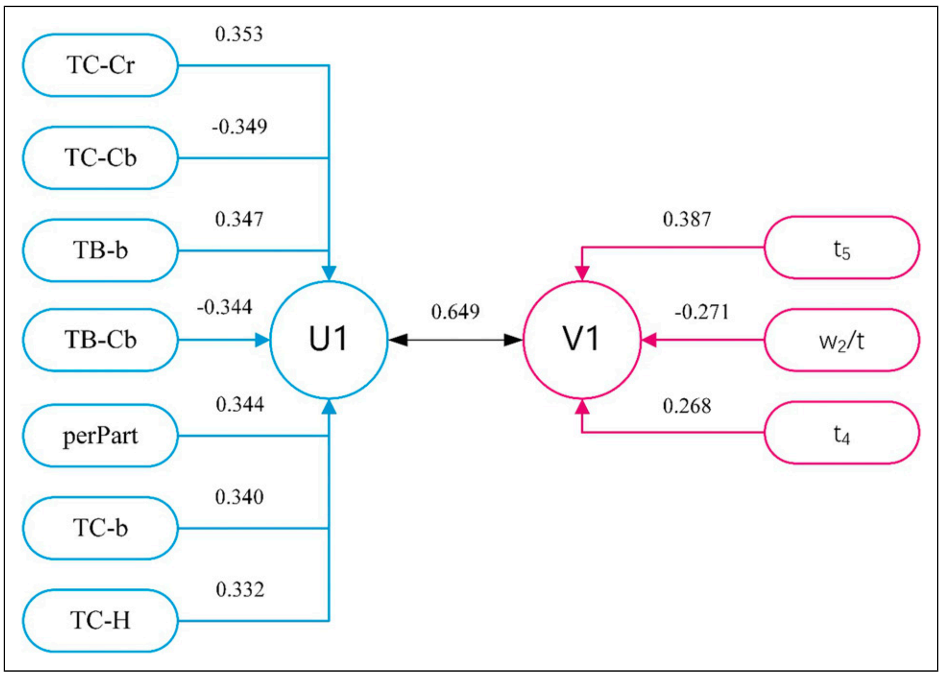

Figure 8. The first canonical correlation variable structure diagram of the tongue and pulse parameters in the disease fatigue group.

pulse data of the sub-health fatigue group have no statistically significant correlation. The pulse parameter t_1 in the healthy controls had a certain correlation with TB-Con, TB-ASM, TB-ENT, and TB-MEAN. And there were more correlated tongue and pulse parameters in the disease fatigue group. The correlation results of tongue and pulse in disease fatigue group showed that w_2/t is closely related to perAll, TC-Cr, TB-b, and TB-Cb, which indicated that the purple or red tongue was closely related to a wiry pulse in disease fatigue group. In addition, the t_1 value of the disease fatigue group was higher than that of the healthy controls and the sub-health fatigue group, and the h_5 value was lower than that of the healthy controls and the sub-health fatigue group, indicating that the myocardial contractility of the disease fatigue group was weakened, and the elasticity of the large artery was weakened, which is mostly a manifestation of heart-qi deficiency in TCM. t_1 was correlated with perAll and perPart, while h_5 was correlated with perAll, indicating that the decreased cardiovascular function in disease fatigue people was closely related to white thick or greasy tongue coating. That is, when the wiry pulse appeared in disease fatigue population, the tongue body was generally blue or red purple, and the tongue coating was generally yellow and thick. When the myocardial contractility was weakened and the heart-qi deficiency, the tongue coating generally white and thick or greasy; when the elasticity of the aorta was weakened, the tongue coating was thick.

Tongue and pulse data correlation analysis using canonical correlation analysis, canonical correlation analysis is a multivariate statistical analysis method to study the correlation between two groups of variables and its basic principle is: in order to grasp the correlation between the two groups of indices on the whole, two representative comprehensive variables U1 and V1 are extracted from the two groups of variables, respectively, and the correlation between the 2 comprehensive variables is used to reflect the overall correlation between the two groups of indices. It borrows the idea of principal component analysis to find one or a few pairs of synthetic variables to replace the original variables according to the correlation between variables, so as to centralize the relationship between two groups of variables into the relationship between a few pairs of synthetic variables. In the result of CCA, in the healthy controls, sub-health fatigue, disease fatigue group, only the disease fatigue group had a canonical correlation between tongue and pulse, showing that fatigue under the influence of disease factor, pulse was associated with tongue more closely compared with the other two groups. The results showed that tongue and pulse of patients with disease fatigue had certain specificity (specific specificity should be further studied for specific diseases), which provided a possibility for diagnosis of disease fatigue. In the disease fatigue group, only the first pair of canonical correlation variables was statistically significant in the canonical correlation analysis, as long as there was one comprehensive variables pair with significant statistical difference, it could indicate that there was some correlation between these two groups of variables. The results of CCA of tongue and pulse showed that the tongue parameters represented by TC-Cr, TC-Cb, TB-b, TB-Cb, perPart, TC-b, and pulse parameters represented by t_5, w_2/t and t_4 were significantly correlated in disease fatigue population. The results indicated that compared with the sub-health group, the tongue parameters in the disease fatigue group were more inclined to purple tongue, deep red tongue, yellow coating, and thick greasy coating. The pulse parameters indicated that the corresponding left ventricular systolic and diastolic period was prolonged, the peripheral vascular resistance was increased and the vascular elasticity was weakened, and these tongue and pulse changes were closely related.

Limitations and Future Research

There were still some limitations in the study. Firstly, all disease fatigue populations were taken as a whole to explore the distribution of their tongue and pulse, lacking of detailed classification of patients with disease fatigue. Different diseases may have different tongue and pulse characteristics. Research on classification of different diseases will be carried out in the future. Secondly, a large-scale and multicenter investigation or prospective studies would be useful for further exploration.

Conclusions

Different fatigue populations have different tongue and pulse data distribution. The development of digital and information technology in the tongue diagnosis and pulse diagnosis provides a convenient, effective, and non-invasive method for the objective diagnosis of fatigue. Four-diagnosis information of TCM provides a good platform for clinical big data research, and will play an increasingly important role in the future clinical diagnosis of disease and syndrome.

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Declaration of Conflicting Interests

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Ethical Consideration

The IRB approved the study protocol of Shuguang Hospital affiliated with Shanghai University of TCM (No. 2018-626-55-01). Written informed consent was obtained from all patients.

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