Systematic Non-Invasive Experimental Analysis of Olfactory Dysfunction using EBG for COVID-19

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***Abstract* - SARS-CoV2 has encompassed showing symptoms from acute respiratory distress syndrome to minor symptoms like loss of smell, taste, fever, body ache. This paper, explains the brain activity observed, if loss of smell (Olfaction) persists. If the symptoms are treated as early biomarker will enable earlier diagnosis and preventative treatments of syndromes. The proposed framework suggests a portable, easy to deploy non-invasive method to detect olfactory dysfunctions at the COVID test center. The validation of the parameters under clinical expertise has laid a ground to predict and proper assess of olfactory deficits in a patient within 20 minutes. The selection of hyper parameters was done using RBF kernel. The test is steered using a simple neuro-imaging, non-invasive device gathering the EBG waves, essentially gamma waves received from the olfactory nerve present in the upper nostril. The results impress to establish a base, that a decreased sense of smell may be a pointer to patients in the initial stage of the syndrome. The statistical validator, Fisher's exact test is performed for data analyses taken from neuroimaging device. The statistical significance was defined as P < .05 for the anosmia (loss of smell). The P- value calculated through our experimental setup is 0.008 for anosmia proved as a significant factor for the detection of infection.**

Keywords—SARS-CoV2, Olfaction, Neuro-imaging device, COVID-19 positive, EBG.

I. INTRODUCTION

SARS-CoV2 has a wide variety of indicators that describe the presence of infection. The infection indicates severe conditions including ARDS [1]. These indicators also specify minor, adequate and asymptomatic forms of the disease which results in spreading infection among human beings over larger geographical locations. The virus penetrates patient's nostrils through ACE2 receptors. This infection damages smell and taste senses as per the authors in 2010 [2]. Olfactory functions are categorized into

- Anosmia: Complete loss of smell
- Hyposmia: Partial loss of smell
- Normosmia: Normal smell sense

As per survey conducted in Wuhan, China, 5.1% out of 214 were having hyposmia during pandemic [3]. Furthers studies have establish an association between olfactory dysfunction and mortality. The studies have shown that patients regain senses within 3-15 days after the onset of virus [4]. Still, little research is being carried out for finding the correlation between the brain waves and olfaction.

A. O1Faction and Brain

The primitive and oldest type of epithelium is the olfactory epithelium. The single dendrite projected from the cell ends in an apical dendritic olfactory knob [4]. The brain is divided as parental Lobe, Frontal Lobe, Occipital Lobe, and Temporal Lobe, this part of the brain is responsible for odour related stimuli [5]. The olfactory cortex [6] responsible for smell- related sense is located in this region as shown in Figure 1. The loss of smell also leads to loss of taste which are outside the scope of this study.

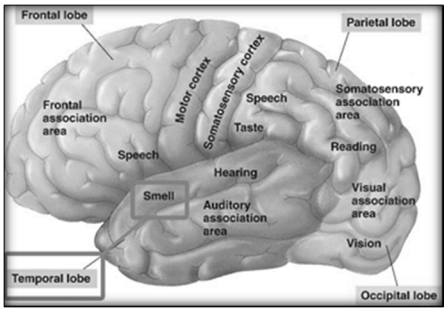

Figure 1: Olfactory in the brain

B. Neuro-Imaging device through EBG

This paper uses a non-invasive, EBG electrode placed over OB, above the eyebrows. Three EEG electrodes are connected to the OB with a precision of a millisecond. The EBG signals are derived via recordings from the EEG electrode from OB, which is coined by the previous researchers as EBG [7]. The EBG signals are derived via recordings from the EEG electrode from OB, which is coined by the previous researchers as EBG. The first experiment involving the relative working of the OB is done on the rodents [8]. The EBG recordings when analysed into different wavelengths having various frequency lengths as shown in Table 1. The waves are activated shortly after 300 ns of the subject has been treated with an odour [7]. Gamma oscillations have a frequency between 30 Hz-100 Hz to detect the intensity of pungent smell.

TABLE I. FREQUENCY BANDS OF DIFFERENT EEG

Brain Waves	Frequency Ranges

Gamma	30Hz-100Hz
Beta	12Hz-30Hz
Alpha	8Hz-12Hz
Theta	4Hz- 7Hz
Delta	<4Hz

II. STATE OF ART

The research on various olfaction methods implemented on the targeted audience to detect the SARS infection are listed in Table 2. This paper focuses on senses involving smell (olfaction) through EBG signals in COVID patients.

TABLE II. STATE OF ART FOR EBG

Author	Olfaction	Method	Targeted Audience	SARS	Findings
[8]	Stimulus, olfactory function	LFP Signals	Rodents, Rabbit, Cat, dog	NO	Odour and memory
[9]	Odour Stimuli	EEG 256 Electrode	Ph.D. students	NO	Self- assessed emotions
[10]	Unpleasantodour	Gamma alpha waves	28	NO	Unpleasant odour
[11]	Olfactory induced EEG	Custom- built olfactometer	28 Graduation students	NO	Time- Frequency analysis of olfaction
[12]	Olfactory event- related potential	EEG and MEG signals	Infants	NO	chemosensory event related potentials (CSERPs)
[13]	Anosmia	local TNF-IL	COVID Patients	YES	OB defense mechanism
[14]	Discriminate Odours	LFP Signals	Rats	NO	Beta rhythm
[15]	SARS virus	Olfactory action meter	COVID Patients	YES	Detection of Covid
[16]	Cognitive neuro-olfactory	EEG signals	Children below 15 years	NO	Chemo- sensory perception
[17]	Acute loss of smell	Survey Questions	Covid Patients	YES	loss of smell
Our work	Anosmia	Survey Question EBG signal	128	YES	Covid classification

The stimulus olfactory function is derived using the LFP signals in rodents [8, 14]. 256 electrodes was used on the Ph.D. students to detect the emotional status relation to the olfaction [9]. The researchers have suggested that unpleasant odour has the relation with frequency of alpha, gamma waves [10]. Authors in [11] experimented on the olfactory event-related potential in the new-born and validated results are presented. Further the olfaction function in relation with the covid patients was studied and the researchers have deriving olfaction as a strong parameter as an early bio-marker to diagnose the virus [15, 17]. A background of the relational status of the operative brain signals and their relevance in percipience of the olfaction or sense of smell is given in Table 2. The deep study of neuroimaging limits to poor resolution of the methods like PET, fMRI as the invasive methods collected noise (artefact) from the sinuses in the nasal area [18]. The waves are activated shortly after 300 ns of the subject has been treated with an odour. It was noted that the gamma bands having frequency range 0 Hz-100 Hz [6] have been visible for a healthy person when given odour onset. Table 3 describes the abbreviations used in the related work.

TABLE III. ABBREVIATIONS USED

Abbreviation	Meaning
ACE2 [18]	Angiotensin-Converting Enzyme 2
ARDS [19]	Acute Respiratory Distress Syndrome
COVID [19]	Corona Virus Disease
EBG [20]	Electrobulbogram
EEG [21]	Electroencephalogram
fMRI [22]	Functional Magnetic Resonance Imaging
IQR [7]	Inter Quartile Range
OB [23]	Olfactory Bulb
OSN [24]	Olfactory sensory neurons
PET	Positron Emission Tomography
PSD	Power Spectral Density
RBF [23]	Radial Bias Function
SARS-CoV2 [25]	Severe Acute Respiratory Syndrome Coronavirus 2
SVM	Support Vector Machine

III. PROPOSED FRAMEWORK

As described in the previous sections the experimentation was carried out with the participants admitted in a hospital under the careful supervision of medical staff. The complete proposed framework is shown in Figure 2. The entire process can be divided into three phases viz:

1. Experimental setup and data gathering
2. Signal processing, Feature extraction
3. Classification

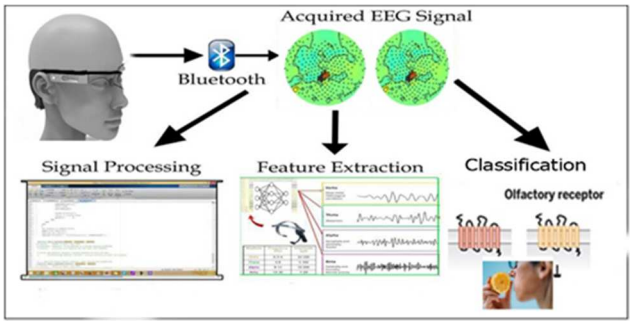

Figure 2: Proposed Framework

A. Experimental setup and data gathering

108 participants COVID-positive patients in the age range of 21 to 90 years were selected. Further the same experiment was conducted on 20 healthy participants also to rationalize the EBG signals obtained from Jan 9, 2021, to Jan 23, 2021, under medical supervision.

This study was conducted in a COVID designated hospital in state of Gujarat, India. The government guidelines in calling the helpline number or registering in Aarogya Setu App was followed for data collection. Participants were informed and educated about the procedure and the drive of the study.

Before the starting the experiment, the participants have signed the consent form. Throughout the experiment, participants were in a hospital controlled environment. The details such as gender, age, travel history, symptoms, nodal officer, date of sample collection, laboratory result were taken. Patients with persistent symptoms were included in the gap interval of 2–7 days.

- *Procedure of odorant experiment*

The patient was made comfortable and asked to breathe normally before the test. An experiment consisted of the three odorants lemon, toothpaste, and Dettol. The odorants were covered to hide the visual imagination of the patients. The experiment was conducted for three sessions to distinguish odour. The odorants were placed 20cm away from the nostrils of the patients and each person was given 3 seconds to inhale. A volunteer was assigned to note the observations and record the answers given by patients over a cart scale of 0-5. A time gap interval of 4 seconds was given to every participant before proceeding to the next session of the test to help the OB to come back to the normal sense. The similar test was conducted on non–covid patients also to ensure the EBG reading accuracy.

The observation from the test suggest that few patients have not experienced the loss of smell or taste as a symptom. Therefore, the patients who complained of loss of smell were considered for the olfactory test. After the interval of seven days, the covid patients reported for loss of smell and taste were again asked to undergo the olfaction test to ensure the regain of the working of OB.

B. Signal Processing and Feature extraction

The signal acquired was collected into a system using a bBluetooth connection. Three EBG electrodes placed on the OB are processed for procuring of signal in a range of 30 Hz-100 Hz [26]. MATLAB programming is used to perform the classifier output result into various wavelengths. The features were extracted from the signal to extract the hyper parameters for olfaction.

The anosmia in the covid patient takes a minimum of 7 days to a maximum of 15 days to regain the olfaction function. The mucous in the nasal region acts as a barrier to the odorants and the OB. Therefore, there is no perception of smell taking place in the brain cells. It is also observed that the higher the PCR Score, the lower is the severity of the virus. Figure 3 depicts the onset of straining of the smell senses working in the brain ranging towards a positive gradient for the three different sessions of the odorant inhalation. The PSD of the signals and the baselines were estimated for frequencies between 30 and 140 Hz, using Welch's non-parametric method with 128 samples. The results were compared to the survey form filled by the patients by using an SVM classifier outputs.

C. Classification Algorithm

SVM classifier with RBF kernel was used to classify the healthy and the infected subjects. This procedure was repeated three times with different odorants. The results are calculated as median and considered for optimization of the attributes. Figure 3 describes the gamma-band oscillations for session 1, session 2, and session 3 for a healthy and a covid positive subject. The measuring scale ranges from -4 to 4 Hz, given different band colours to show the intensity of odour perceived in the brain through EBG signals. The median for the continuous variables was depicted using the median with IQR. The Likert scale values of 5 to 4 are considered as severe, values of 3 to2 are considered as moderate, 1 to 0 is taken as mild.

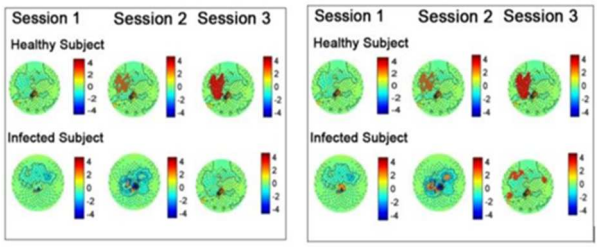

Figure 3: Gamma Waves for healthy versus infected in span of 3 and 7 days

IV. RESULTS AND DISCUSSION

The self-evaluation form is filled by the volunteers observing the symptoms and the patient explanation in form of a Likert

scale of 1 to 5, 1 being the less symptomatic and 5 being the highest symptomatic. Further, 12 healthy participants were also examined and no symptoms or disorders in the brain waves were observed. The symptoms observed are in form of a Likert scale of 0-5, the categorical parameters were compared with a Fisher's Exact Test [27]. Equation 1 is used for establishing statistical significance between categorical variables.

$$P = \frac{(u+v)!\,(\omega+x)!\,(u+\omega)!\,(v+x)!}{u!\,v!\,w!\,x!\,N!} \qquad (1)$$

Gamma rays from the EBG raw signals are used for calibration and testing. In the calibration step, a further phase, consisting of the labelling of some trials, was performed to indicate to whose signals corresponded 4 and to who's corresponded -4.

A. Statistical Derivations

A total of 128 covid patients admitted to the COVID hospital under different symptomatic conditions (83 women) aged from 21 to 90 years (mean age: 61±3 years) participated in the research. Table 4 presents the statistical derivations of symptoms for SARS-COVID 19 includes chills out of 128 patients 34 (26%) reported having cold severing with 21 (16%) mild chills, 61 (47%) having moderate 44 (34%) having severe chills. The corresponding P-value is calculated as 0.52, compared to the alpha value is very insignificant.

Cough as a symptom out of 128 patients, 2 (0.19%) mild, 2 (0.19%) moderate 100 (96%) having a severe cough. The corresponding P-value is calculated as 0.052 significant many of the patients developed a dry cough at the onset of the virus.

Fever 128 (97%) reported among the 128 patients with 2 (0.16%) mild temperature, 2 (0.16%) moderate temperature of 98 Celsius, 124 (85%) having high degrees. The corresponding P-value is calculate as <0.0001*, 8.68 (3.44-21.93).

Sputum in 62 (48%) reported having congestion of 7 (11%) mild symptoms, 5 (0.08%) having moderate sputum, 50 (80%) having severe congestion. The corresponding P- value is calculated as 0.1552, suggesting no significance of having sputum with the virus.

Loss of smell out of 128 patients 64(51%) reported having normosmia 2 (0.03%), 10 (15%) having anosmia, 54 (84%) having hyposmia. The corresponding P-value is calculated as 0.023, showing the relative significance of the loss of smell as the main neurological symptoms of the sensory neurons that detect and transmit the sense of smell to the brain are blocked by the mucus formed by the virus.

Sore throat in 128 patients, 97(75%), 12(12%) mild pain in the throat, 15(15%) having moderate 70(72%) having severe. The corresponding P-value is calculated as 0.244. Chest pain out of 128 patients 87(67%) reported 12(13%) mild pain, 25(28%) having moderate 50(57%) having severe pain in the chest. The corresponding P-value is calculated as 0.768.

Runny nose out of 128 patients, 55 (42%) reported with 15 (27%) mild symptoms, 10 (18%) having moderate, 30 (54%) having severe. The corresponding P-value is calculated as 0.817. The P-value is greater than the alpha value showing no significance with the virus spread.

Nasal stuffiness out 128 patients 115 (89%) reported having with 15 (13%) mild, 20 (17%) having moderate 80 (69%) having severe. The corresponding P-value is calculated as 0.006.

Chest discomfort in 128 patients 82 (64%) reported with 15 (23%) mild discomfort, 25 (39%) having moderate 42 (65%) having severe discomfort. The corresponding P-value is calculated as 0.043.significance of the virus to be present.

Shortness of breath out of 128 patients 40 (31%) reported with 10 (25%) mild, 5 (0.12%) having moderate 25 (62%) having severe breathlessness.

Body Ache among patients 30(23%) reported having 10(33%) mild aches, 5(0.16%) having moderate 15(50%) having severe aches. The corresponding P-value is calculated as 0.615.

Loss of taste in 128 patients 79 (61%) reported having 4 (0.3%) mild symptoms, 15 (18%) having moderate 60 (75%) having severe. The corresponding P-value is calculated as 0.0512.

Loss of appetite out 85(66%) reported having with 15(17%) mild, 20(23%) having moderate 50(58%) having severe. The corresponding P-value is calculated as 0.81.

Nausea out of 128 patients 53(0.7%) reported 18(33%) mild, 15(28%) having moderate 20(37%) having severe. The corresponding P-value is calculated as 0.64.

Vomiting out of 128 patients 42(32%) reported having with 12(28%) mild feeling, 15(35%) having moderate 15(35%) having severe. The corresponding P-value is calculated as 0.72.

Abdominal pain out of 128 patients 45(35%) reported having pain with 15(33%) mild, 10(22%) having moderate 20(44%) having severe. The corresponding P-value is calculated as 0.85.

Diarrhea out of 128 patients 25(19%) reported having 10(40%) mild, 5(20%) having moderate 10(40%) having severe. The corresponding P-value is calculated as 0.64. Constipation out of 128 patients 22(17%) reported having cold severing with 2(9%) mild, 5(22%) having moderate 15(68%) having severe. The corresponding P-value is calculated as 0.67.
Arthralgia out of 128 patients 40(31%) reported having with 10(25%) mild, 10(25%) had moderate 20(50%) had severe joint pains.

TABLE IV. THE STATISTICAL OBSERVATIONS FOR THE CATEGORICAL PARAMETERS USING FISHER'S EXACT TEST

Healthy Subjects (12)	All Patients (N=128)	Mild	Moderate	Severe	P-value
Variables					
Age	128 (21-80)	68 (53%)	50(39%)	10(7%)	0.052
Sex					
Male	44(34%)	17(38%)	20(45%)	7(15%)	_
Female	83(64%)	36 (43%)	47(56%)	2(2%)	_
Symptoms					
Chill	34(26%)	21 (16%)	61(47%)	44(34%)	0.52
Cough	104(81%)	2(0.19%)	2(0.19%)	100(96%)	0.052*
Fever	128(97%)	2(0.15%)	2(0.15%)	124(85%)	0.014*
Sputum	62(48%)	7 (11%)	5(0.08%)	50(80%)	0.155
Lost smell	64(51%)	2(0.03%)	10(15%)	54(84%)	0.023*
Sore throat	97(75%)	12 (12%)	15(15%)	70(72%)	0.244
Runny nose	55(42%)	15 (27%)	10(18%)	30(54%)	0.817
Nasal stuffiness	115(89%)	15 (13%)	20(17%)	80(69%)	0.006*
Chest pain	87(67%)	12 (13%)	25(28%)	50(57%)	0.76 8
Chest discomfort	82(64%)	15 (23%)	25(39%)	42(65%)	0.043*
Shortness of breath	40(31%)	10 (25%)	5(0.12%)	25(62%)	0.034*
Body ache	30(23%)	10 (33%)	5(.16%)	15(50%)	0.615
Loss of Taste	79(61%)	4 (0.3%)	15(18%)	60(75%)	0.512
Loss of appetite	85(66%)	15 (17%)	20(23%)	50(58%)	0.81
Nausea	53(0.7%)	18 (33%)	15(28%)	20(37%)	0.64
Vomiting	42(32%)	12 (28%)	15(35%)	15(35%)	0.72
Abdominal pain	45(35%)	15 (33%)	10(22%)	20(44%)	0.85
Diarrhea	25(19%)	10 (40%)	5(20%)	10(40%)	0.64
Constipation	22(17%)	2 (9%)	5(22%)	15(68%)	0.67
Arthralgia	40(31%)	10 (25%)	10(25%)	20(50%)	0.42

B. Results derived from Reading Brain Map

The patients who had the loss of smell as a major symptom, derived P-value is less than 0.5. It proves there is a strong significance relation between olfaction and the virus onset. The patient is given three sessions on the next day of admission to the hospital. The first day is spent in observation of the symptoms by the volunteers. In the three sessions we have used three different odorants and the differences in median values were assessed using the Mann-Whitney-Wilcoxon Rank Sum Test for the parametric test factors to find the P-value for the sampling distribution. The Mann-Whitney U test is a non- parametric test in which the data in each group are first ordered from lowest to highest. The brain imaging waves of raw signal collected from 30-120 Hz. as shown in Figure 4.

Values in the entire data set, from both the control and treated groups, are then ranked, with the average rank being assigned to tied values as it is for the Wilcoxon rank-sum test [28]. Values of p less than 0.05 were considered to be statistically significant. Multivariate logistic regression models were constructed to identify factors associated with severity of symptoms.

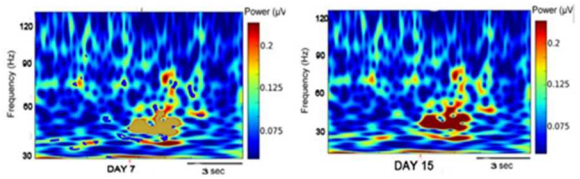

Figure 4: Brain Map for the Mann-Whitney Test

The ranks are then summed for each group, and U is determined. The calculation process uses Equation 2 and Equation 3.

$$U_t = n_c n_t + \left\{\frac{n_t(n_t+1)}{2}\right\} - R_t \qquad (2)$$

$$U_c = n_c n_t + \left\{\frac{n_c(n_c+1)}{2}\right\} - R_c \qquad (3)$$

The comparison of the P-value to the alpha value done to check the significance of the result. 2 –tailed test is conducted for each session of the brain waves is shown in Table 5. PID

is patient id and S-1, S-2, S-3 are sessions. The statistical analyses were done using SPSS.

The following steps for analysis are followed

1. Sessions of Day 2 and Day 7 were divided into three odorants given to the patients with an interval of 4 seconds not concealing the odorant, to avoid visual imagination.
2. The average mean of the sessions was calculated
3. The ranking of the raw signals was calculated on the rating received by the Average mean of the readings
4. Mean (637.5), Standard Deviation (51.5388) and Z-value (2.39625), P-value (0.008) is determined consequently.

TABLE V. THE STATISTICAL RESULTS BASED ON WHITNEY SUM RANK 2-TAILED TEST

DAY 7					DAY 15					
ID	S1	S2	S3	Mean	S1	S2	S3	Mean	Rate	Rank
PD 1	22	30	32	28	60	45	84	63	28	80
PD 2	25	58	25	36	55	68	74	66	36	130
PD 3	40	42	95	59	74	84	72	77	59	152
PD 4	32	35	25	31	85	87	88	87	31	117
PD 5	24	25	27	25	45	75	89	70	25	26
PD 6	24	21	28	24	47	78	75	67	24	10
PD 7	23	25	29	26	55	58	59	75	26	31
PD 8	25	24	32	27	71	76	72	59	27	52
PD 9	48	97	85	77	64	65	67	72	77	214
PD 10	21	27	34	27	72	71	79	67	27	58
PD 11	35	28	28	30	84	82	81	79	30	109
PD 12	24	29	10	21	59	58	57	81	21	4
PD 13	25	21	82	43	85	84	87	57	43	124
PD 14	24	17	21	21	79	89	94	87	21	1
PD 15	25	23	22	23	74	75	79	94	23	4
PD 16	40	24	25	30	65	68	67	79	30	96
PD 17	35	27	26	29	68	67	62	67	29	91
PD 18	21	28	91	47	78	75	79	62	47	123
PD 19	24	29	25	26	82	84	85	79	26	32
PD 20	22	30	23	25	87	81	80	85	25	18
PD 21	23	23	27	24	74	87	81	80	24	7
PD 22	25	58	28	37	78	75	76	76	37	115
PD 23	24	34	32	30	84	85	84	84	30	97
PD 24	25	35	34	31	78	85	87	83	31	105
PD 25	10	36	35	27	79	86	82	82	27	46
PD 26	29	37	31	32	94	78	85	86	32	105
PD 27	37	38	25	33	75	84	85	81	33	109
PD 28	28	39	24	30	82	86	94	87	30	99
PD 29	37	21	25	28	79	76	72	76	28	63
PD 30	28	22	26	25	84	89	83	85	25	20
PD 31	37	2	27	30	65	64	62	64	30	89

V. CONCLUSION

This study demonstrates an economical, portable olfactometer to study the olfactory function by generating a self-activated EBG signal using SVM classification. This neuro-imaging non-invasive, device helps to identify the olfactory function while subjected to odorants for 108 COVID-positive patients and 20 healthy persons. The confirmation of OB engrossment in COVID-19 remains uncommon in many research works, but the familiarity of this different way of spreading could lead to developments in the management of SARS-CoV2 patients with anosmia if used as a detector tool. The acquired EBG signals were studied to extract the patterns that immerse during olfactory perception. The results of this study show that when training a classifier with the data from patients separately who complained of the symptoms of loss of smell. A moderately high classification accuracy can be obtained giving a significant P-value. The results stating that anosmia in patients, if not treated at an early stage will lead to acute respiratory problems. The observation of Whitney Sum Rank 2-tailed Test suggests the mean as 637.5, SD as 51.5388, Z-Value is 2.39625, the P-value is 0.008. The virus from the nasal activity in the form of mucous can travel into the lungs in the respiration process. A future extension of the current work could be to repeat the same test with more subjects to obtain more brain activity patterns. Another interesting future direction is to use many odorant stimuli ranging and the ECG signals from the heart can be monitored. The signals can be fed into a mobile for continuous monitoring of patient recovery. The methodology introduced in this paper can be repeated to explore the feasibility of accurate classification of heartbeat irregularity using EBG and ECG signal processing.

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