Effects of Auricular Vagus Nerve Stimulation on Voice Characteristics
Auriküler Vagus Sinir Stimülasyonunun İnsan Ses Özelliklerine Etkileri

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***Abstract*—Vagus nerve stimulation (VNS) has been used in the treatment of epilepsy and depression for more than 20 years. Although the invasive cervical method is the most preferred application, side effects such as cough, voice change and hoarseness can be seen due to negative effects on the recurrent laryngeal nerve (a branch of the vagus nerve). Auricular VNS has been preferred recently due to its non-invasiveness, but uncertainty about the stimulation parameters continues. We tested the hypothesis that auricular VNS can affect voice and its features indirectly via afferent nerve connections reaching the nucleus tractus solitarius. Two patients previously using auricular VNS device for different diseases were requested to record their voices before and after the stimulation. Their devices (Vagustim™) were changed with new version to check the usage of the patients. Sound recordings at different VNS frequencies (1-150 Hz) were collected by a mobile phone and analyzed with Praat and our MATLAB algorithm. Fundamental frequency (f0), jitter, shimmer, and harmonic to noise ratio (HNR) owere evaluated. The alteration was highest at 100 Hz and 30 Hz VNS for the male and female patients respectively. Audio recordings before and after 30 Hz (for female) and 100 Hz (for male) VNS at different durations (5-30 min) on different days were repeated and compared by Praat and our algorithm. Some discrepancy between the parameters jitter, shimmer, and HNR are detected between the algorithms, which is accounted to the fact that it is not standardized whether the algorithm uses only a specific part of the input signal or the whole signal. However, when the ratio of change of these parameters are considered, fundamental frequency and the HNR were found to be highly consistent for developing an algorithm to govern the stimulation parameters in an automated way. Furthermore, the same ratios for jitter and shimmer are also promising after some improvement to be included in such an algorithm. These results suggest that auricular VNS can affect voice and its parameters, but this change is related with stimulation parameters. It seems necessary to develop specific software and algorithms that can detect this change well.**

Keywords*—auricular vagus nerve stimulation; parameter optimization; sound analysis; algorithm; software

***Özetçe*—Vagus sinir uyarımı (VSU), epilepsi ve depresyon tedavisinde 20 yılı aşkın süredir kullanılmaktadır. İnvaziv servikal yöntem en çok tercih edilen uygulama olmasına rağmen rekürren laringeal sinir (vagus sinirinin bir dalı) üzerindeki olumsuz etkilerinden dolayı öksürük, ses değişikliği ve ses kısıklığı gibi yan etkiler görülebilmektedir. Auriküler VSU, non-invaziv olması nedeniyle yakın zamanda tercih edilmeye başlanmıştır, ancak stimülasyon parametreleriyle ilgili belirsizlik devam etmektedir. Auriküler VSU'nun nükleus traktus solitarius'a ulaşan afferent sinir bağlantıları yoluyla sesi ve özelliklerini dolaylı olarak etkileyebileceği hipotezini test ettik. İki yazar auriküler VSU cihazını (Vagustim™) kullandılar ve stimülasyondan önce ve sonra seslerini kaydettiler. Farklı VSU frekanslarındaki (1-150 Hz) ses kayıtları bir cep telefonu ile toplanmış ve Praat yazılımı ve MATLAB algoritmamız ile günlük olarak analiz edilmiştir. Sesin temel frekansı veya perdesi (f0), jitter, shimmer ve harmonik gürültü oranı (HNR) değerlendirildi ve değişiklik her birey için 100 Hz ve 30 Hz'de (VSU frekansı) en yüksek bulundu. Bir birey için 30 Hz VSU ve diğer birey için 100 Hz, farklı sürelerde (5-30 dk) VSU öncesi ve sonrasında farklı günlerde ses kayıtları tekrarlanarak Praat ve algoritmamız ile karşılaştırılmıştır. Algoritmalar arasında jitter, shimmer ve HNR parametreleri arasında bir miktar tutarsızlık tespit edildi; bu durumun, algoritmanın, sinyalin yalnızca belirli bir kısmını mı yoksa tüm sinyali mi kullandığının standartlaştırılmadığı gerçeğine bağlı olduğu düşünüldü. Bununla birlikte, bu parametrelerin değişim oranı göz önüne alındığında, temel frekans ve HNR'nin, stimülasyon parametrelerini otomatik bir şekilde yönetmek ve bir algoritma geliştirmek için oldukça tutarlı olduğu bulundu. Ayrıca, jitter ve shimmer için benzer oranlar da, böyle bir algoritmaya dahil edilecek bazı iyileştirmelerden sonra umut verici olabilir. Bu sonuçlar auriküler VSU'nun sesi ve parametrelerini etkileyebileceğini, ancak bu değişikliğin stimülasyon parametreleriyle ilgili olduğunu düşündürmektedir. Bu değişikliği iyi tespit edebilecek spesifik yazılımlar ve algoritmalar geliştirmek gerekli görünmektedir.**

Anahtar Kelimeler*—auriküler vagus sinir stimülasyonu; parametre optimizasyonu; ses analizi; algoritma; yazılım

I. Introduction

As a neuromodulation method, vagus nerve stimulation (VNS) was first used in the treatment of drug-resistant epilepsy and in more than 20 years of study, VNS has consistently demonstrated its efficacy. Adverse events with VNS treatment are rare and include surgical adverse events (infection, vocal cord paresis, etc.) and stimulation side effects (hoarseness, voice change, cough). There is a need for the development of VNS, like closed-loop and non-invasiveness, to reduce side effects and increase efficacy [1]. In cervical invasive VNS, electrode of the device that wraps the vagus nerve, stimulation itself and surgical complications can affect vocal cords and voice. Hoarseness is the most common side effect after the VNS implantation. VNS can affect the voice and reduce vocal cord motion on the implantation side. Laryngeal side effects seem to be proportional to the current amplitude, frequency and duration of stimulation [2], [3]. In contrast to non-invasive VNS methods (cervical and auricular), invasive procedure is associated with laryngeal muscle activation and induces voice modifications, well-known side effects of the therapy resulting from co-activation of the recurrent laryngeal nerve (a division of vagus nerve for larynx muscles and voice production). This situation causes laryngeal motor evoked potentials and it might be useful as a marker of effective nerve activation, and as an aid for the clinician to perform a more rational titration of VNS parameters [4]. Sound analysis might also be used to evaluate VNS but the knowledge is less and there are dissimilar opinions about its acceptance. Kochilas et. al. used jitter, shimmer, and harmonic-to-noise ratio as vocal measures and said that electrical stimulation of the vagus nerve had no long-term adverse effects on vocal function [5]. However, Charous et. al. declared that hyperstimulation of the affected vocal cord was observed during vagal stimulation with paramedian positioning, vocal fold tensing, and loss of mucosal wave. Increase in jitter and shimmer was consistent while the epilepsy patients were under stimulation. Vagal nerve implantation devices create significant but well-tolerated vocal side effects [6]. It can be seen that the change in voice is mostly interpreted as a side effect of VNS components [7], [8]. Kersing et. al. analyzed phonation in epilepsy patients during VNS and detected slight increase in mean fundamental frequency [9]. Saibene et. al. found a significant increase in the values of jitter, shimmer and noise-to-harmonic ratio during VNS activation in their study with epilepsy patients and stated that acoustic analysis was deteriorating [10]. In the study of Van Lierde et al., jitter, shimmer and harmonics-to-noise ratio values were high in VNS group without stimulation (in rest condition) according to control group. During stimulation the fundamental frequency is significantly increased in VNS group [11]. Dyspnea and dysphonia, can persist even with VNS deactivation in invasive cervical method so the change in voice is not only related with stimulation [12]. Both implantation and stimulation-related side effects can be seen in epilepsy patients receiving VNS treatment. The adverse effects appear to be due to recurrent laryngeal nerve paralysis related vocal cord hypofunction and stimulation related vocal fold spasms [13]. Furthermore it is stated that VNS can reduce vocal cord motility and recurrent laryngeal nerve stimulation can be used for laryngeal dystonias [14], [15].

Auricular VNS is a new method compared to its invasive counterpart and has minimal (redness, itching on the ear) side effects. It has been used and investigated for several disorders, including epilepsy, depression, chronic pain, and inflammation. Beside the little side effects, auricular VNS is also noninvasive, so the surgical complaints do not exist. Tragus and concha regions are mostly innervated by the auricular branch of the vagus nerve and the afferents originating from this area terminate on the nucleus tractus solitarius like the cervical branch [16]–[19]. The present case study was planned to investigate the effects of auricular VNS on sound parameters. We tested the hypothesis that auricular VNS can make a change on voice and whether this change is dependent to stimulation parameters or not. In addition, we created an algorithm and compared it with a known sound analysis software afterwards.

II. Methods

A. Clinical Characteristics of the Subjects

Two patients participated in the study. The male was 39 years old and has been using Vagustim device (Fig. 1), unregularly for tension type headache for three years. He had been applying the therapy one or two times per week and 20 or 30 minutes for one session. The 36 years old female patient was using the same device for bruxism and left temporomandibular joint disorder. She stated that she had no jaw pain during the 6 months of using the device and she was applying it twice a week for 20 minutes.

B. Procedures

The subjects were informed of the intervention and they agreed to record audio and free exchange with new versions of devices. The new version of the device is used to check the usage of the patients (Fig. 1). The new device is controlled by a mobile app and the stimulation data can also be collected. The stimulation was applied from tragus and concha regions as bilateral, biphase, and with 300 μs pulse duration. The patients were requested to record their voices before and after the stimulation and do one treatment per day. Sound recordings at different VNS frequencies (1-150 Hz) were collected by a mobile phone and analyzed in a daily routine with Praat software and our MATLAB algorithm. The samples for testing the algorithm against Praat are simply human voice recordings while reading out the sound "a" for 5-10 seconds. These samples were collected using smartphones as mono sound with 48kHz sampling rate. Voice changes were highest at 100 Hz and 30 Hz (frequency of the VNS) for the male and female patients respectively. In addition, as the duration increases, the female patient started to report nausea at 30 Hz and the male patient started to report fullness in the ear at 100 Hz. Therefore, audio recordings before and after 30 Hz (for female) and 100 Hz (for male) VNS at different durations (5-30 min) on different days were repeated.

III. Results

In the assessment of the effect of auricular vagus stimulation on human voice characteristics, four parameters of voice were taken into account. These are namely the fundamental frequency or pitch (f0), jitter, shimmer, and harmonic to noise ratio (HNR).

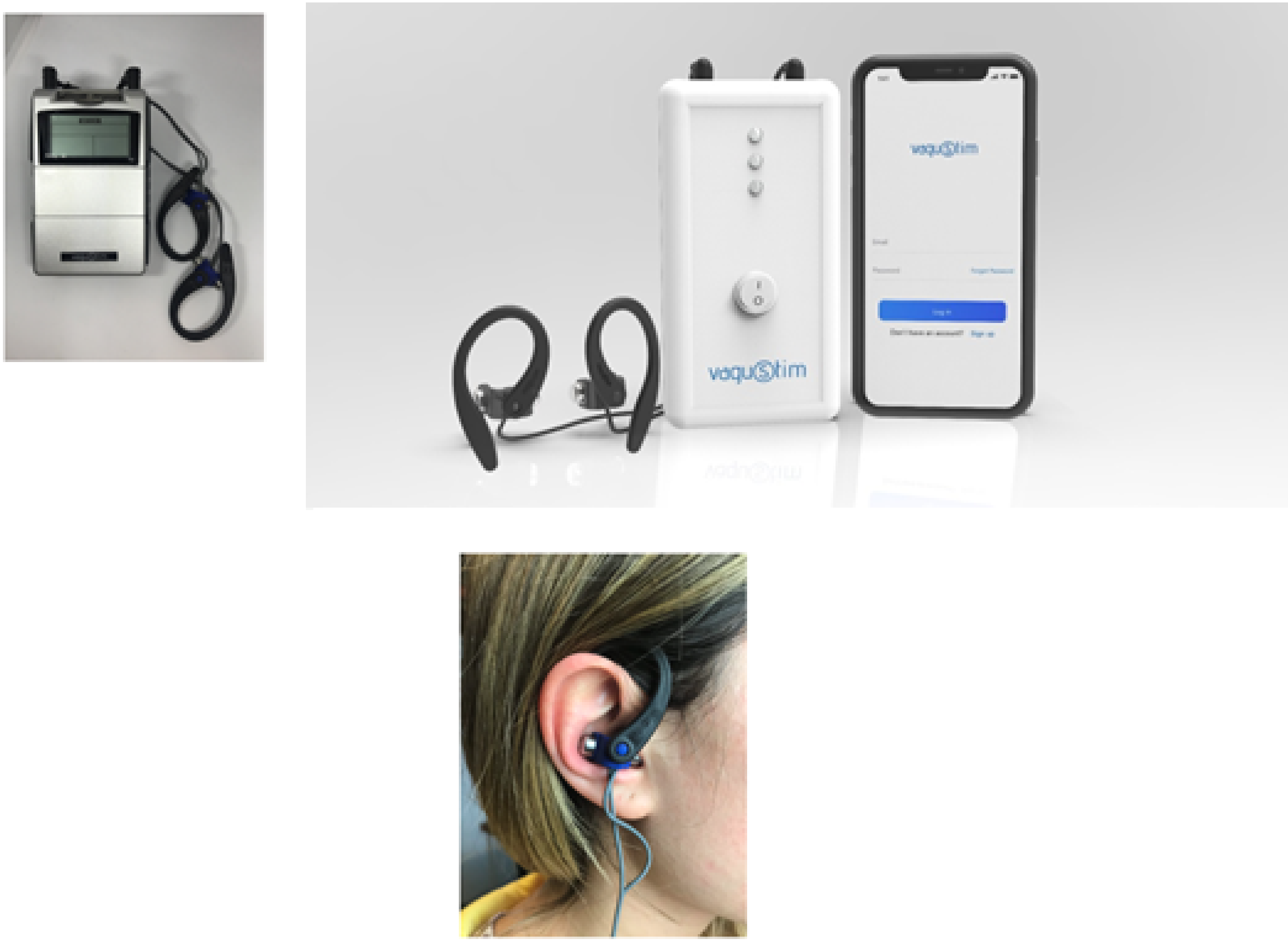

Figure 1: Vagustim device used in the study. The older version is on the top left and the used version is on the top right. The application on the ear is shown on the bottom

Among these parameters, f0 is simply the number of times the sound wave is produced per second. This parameter may differ depending on many different factors including the gender, age, and health conditions, and even time of the day or state of mind. Jitter and shimmer, on the other hand, are two different parameters related to the disturbances in the frequency and the amplitude, respectively, of the produced sound. While jitter defines the amount of the change in the successive periods in the sound signal, shimmer measures the amplitude variation of the same (Fig. 2). Finally, harmonic to noise ratio measures the power ratio between the harmonic components of the sound signal and the noise components.

For all these parameters, the widely used sound analysis software Praat provides different types of calculations. In the case where the fundamental frequency is of consideration, there is only the mean, median, minimum and the maximum values of the pitch detected, and also the standard deviation calculated. However, for jitter, shimmer, and HNR, there are different ways of representation. While all these different ways of calculations basically measure the same characteristics, the main difference stems from the ways of expressing the measurement. As an example, the jitter can be expressed as local, absolute which is the average variation of the period given in μs, whereas local jitter gives the same average period variation as the percentage of the average period. In this work, since the main goal is to develop an algorithm based on detection of the voice characteristics from sound records rather than duplicating Praat results, only one type of calculation for each parameter is chosen. We expressed the pitch as the median pitch, jitter as local, absolute jitter, shimmer as local (%) and finally calculated the harmonic-to-noise ratio in dB.

In order to extract these parameters using the custom MATLAB algorithm, we used the audio toolbox and signal processing toolbox of MATLAB along with the basic functions. The stimulation frequencies are set to 30 Hz for female and 100 Hz for the other, after a scan of the available frequency ranges by the used device. Afterwards, the pitch of these mono-sounds were extracted using the built-in functions in

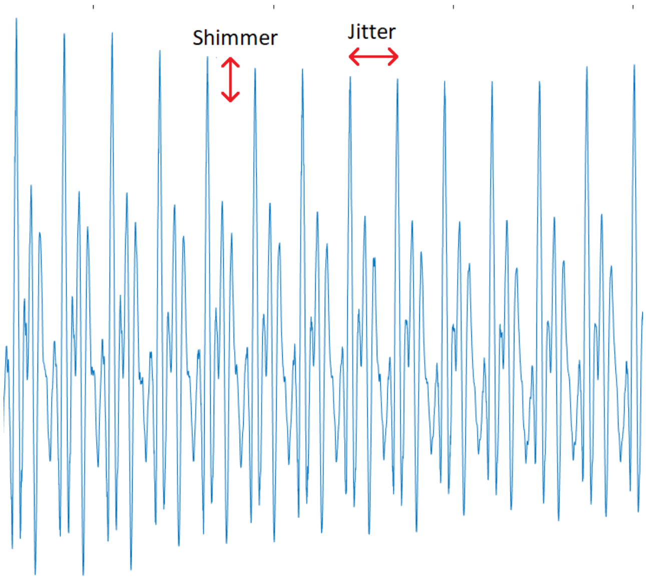

Figure 2: Jitter and shimmer representation

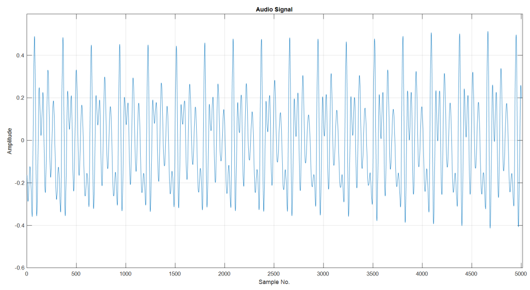

Figure 3: A 200ms segment of the speech signal

audio toolbox. The extraction of the pitch is followed by finding out the jitter, shimmer, and the HNR of the speech signal. In order to calculate these parameters, the signal is first divided into segments of 200ms (Fig. 3). This is done in order to make the detection of the sound peaks, which correspond to the exact moments of sound production easier. Then, the jitter and shimmer of each segment is calculated by finding the aforementioned peaks, and using these peaks to detect the consecutive variations of amplitude and period. In the following step, this speech segment is translated into the frequency domain using Fourier transform in order to calculate HNR. On this frequency spectrum, as suggested by Shama et.al., only the harmonics lower than 5 kHz were taken into consideration and the rest of the spectrum is considered as noise signal [20]. Furthermore, for the simplicity of calculations, it is assumed that harmonic part and the noise part do not have any contribution to each other. This way, the calculations are done for each segment and stored in an array assigned to each parameter. After scanning through all these segments, the average jitter, shimmer, and HNR of these segments are provided as the resultant values.

In the comparison between the MATLAB algorithm and Praat software, we kept two things in mind. Firstly, different algorithms can work on different ways in terms of the used segment of the input voice. That is, while some algorithms use the whole input signal to calculate the sound characterization parameters, others choose to stay on the safe side by analyzing the most stable part, which mostly coincides with the middle part of the signal. Secondly, as mentioned earlier by Oller and Ternström, for the case of HNR calculation, even the formulation is not standard [21]. Considering these two facts, and without clear information on the algorithm of Praat, we did not compare the exact results of jitter, shimmer, and HNR with the Praat results. We calculated the ratio between before and after the stimulation for each parameter. In Fig. 4 and Fig. 5, it can be seen clearly that auricular vagus stimulation affects the characteristics of the voice signal. On the other hand, in Fig. 6 and Fig. 7, the comparison between the change ratios obtained in each parameter can be found. These foundings can also be observed in Table I and Table II.

Figure 4: Change in voice parameters with 30Hz stimulation. Numbers 1-8 denote the trial number

Several deductions can be made from the data presented in these figures and tables. First of all, it is clear that auricular vagus stimulation causes some changes in the parameters which determines the characteristics of the voice signal. However, it is still necessary to analyze how these changes occur. Secondly, if we compare the calculations by two algorithms parameter by parameter, it is clear that the best performance of the custom audio analysis algorithm is achieved in detecting the fundamental frequency of the signal. This is followed by the HNR findings, where the largest difference between Praat and our algorithm is below 15%, and the average is only 6.13%. The average difference for jitter and shimmer measurements, on the other hand, are 24.18% and 21.15%, respectively. These values are summarized in Table III.

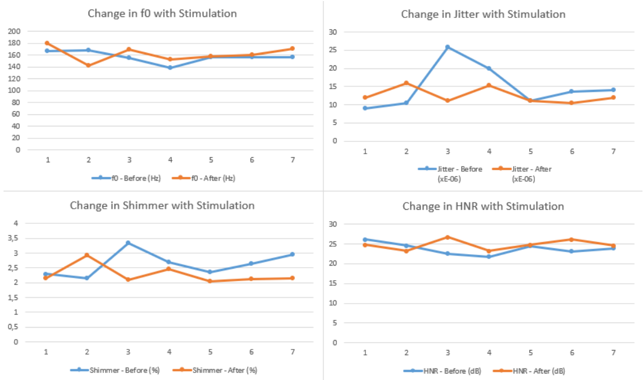

Figure 5: Change in voice parameters with 100Hz stimulation. Numbers 1-7 denote the trial number

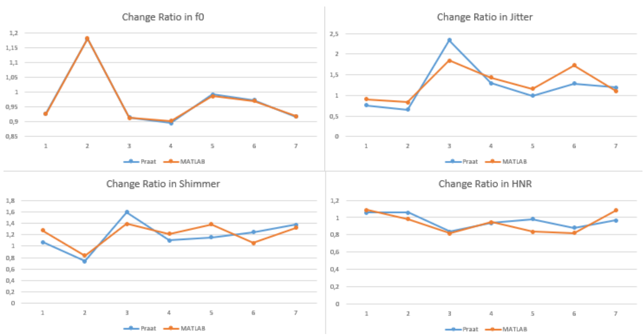

Figure 6: Change ratios in all four parameters via Praat and the custom MATLAB algorithms for user 1, where stimulation frequency was 100Hz

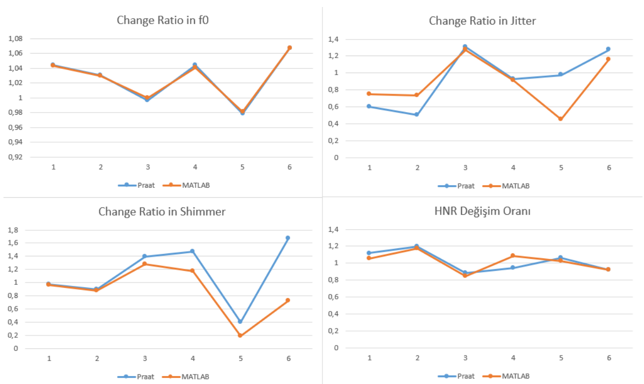

Figure 7: Change ratios in all four parameters via Praat and the custom MATLAB algorithms for user 2, where stimulation frequency was 30Hz

Measurement Number	f0 Ratio (Praat)	f0 ratio (MATLAB)	f0 Ratio Diff. (%)	Jitter Ratio (Praat)	Jitter Ratio (MATLAB)	Jitter Ratio Diff.	Shimmer Ratio (Praat)	Shimmer Ratio (MATLAB)	Shimmer Ratio Diff.	HNR Ratio (Praat)	HNR Ratio (MATLAB)	HNR Ratio Diff.
1	0.9284	0.9268	0.1667	0.7576	0.9128	20.4835	1.0701	1.2719	18.8616	1.0593	1.0890	2.8023
2	1.1815	1.1825	0.0843	0.6568	0.8395	27.8037	0.7363	0.8339	13.2566	1.0563	0.9832	6.9249
3	0.9145	0.9126	0.2030	2.3449	1.8445	21.3379	1.5905	1.3853	12.8990	0.8357	0.8170	2.2346
4	0.9016	0.9023	0.0726	1.2987	1.4398	10.8629	1.0979	1.2165	10.7919	0.9366	0.9456	0.9548
5	0.9861	0.9869	0.0837	0.9946	1.1633	16.9560	1.1519	1.3801	19.8036	0.9847	0.8382	14.8794
6	0.9731	0.9707	0.2432	1.2909	1.7272	33.7893	1.2406	1.0562	14.8631	0.8812	0.8212	6.8058
7	0.9175	0.9186	0.1163	1.1894	1.1081	6.8342	1.3721	1.3196	3.8232	0.9664	1.0833	12.0963

Table I: The maximum and average differences detected between two algorithms for each parameter

Measurement Number	f0 Ratio (Praat)	f0 ratio (MATLAB)	f0 Ratio Diff. (%)	Jitter Ratio (Praat)	Jitter Ratio (MATLAB)	Jitter Ratio Diff.	Shimmer Ratio (Praat)	Shimmer Ratio (MATLAB)	Shimmer Ratio Diff.	HNR Ratio (Praat)	HNR Ratio (MATLAB)	HNR Ratio Diff.
1	1.0438	280.7000	1.0427	0.5998	0.7478	24.6770	0.9688	0.9674	0.1403	1.1176	1.0538	5.7043
2	1.0303	277.4600	1.0297	0.5063	0.7310	44.3752	0.8923	0.8794	1.4429	1.1945	1.1771	1.4557
3	0.9965	311.6900	1.0000	1.3084	1.2679	3.0952	1.3898	1.2789	7.9808	0.8834	0.8443	4.4313
4	1.0441	311.6900	1.0405	0.9288	0.9100	2.0211	1.4713	1.1709	20.4127	0.9422	1.0834	14.9944
5	0.9785	307.6900	0.9811	0.9744	0.4481	54.0164	0.3993	0.1909	52.1801	1.0617	1.0274	3.2376
6	1.0673	274.2900	1.0671	1.2735	1.1582	9.0503	1.6692	0.7282	56.3743	0.9175	0.9223	0.5262
7	1.0438	280.7000	1.0427	0.5998	0.7478	24.6770	0.9688	0.9674	0.1403	1.1176	1.0538	5.7043

Table II: Before/after ratios of each parameter and the difference between two algorithms for the measurements with user 2 at 30Hz stimulation frequency

Parameter	Maximum Difference (%)	Average Difference (%)
f0 Ratio	0.36	0.16
Jitter Ratio	63.26	24.18
Shimmer Ratio	63.32	21.15
HNR Ratio	14.99	6.13

Table III: The maximum and average differences detected between two algorithms for each parameter

IV. Conclusions

By using the present data, it is not possible to thoroughly understand how each voice parameter changes after a successful stimulation. However, it is clear that there exists a difference which is detectable by sound analysis algorithms. This affirms the claim that autonomic nervous system activity change is associated with voice characteristics [20]. Auricular VNS most probably affects the autonomic nervous system activity and causes the changes in the voice as in this study. Developing specific software and algorithms can help to understand and predict this change in the future. By the present data, it is fair to say that an algorithm can be built to personalize stimulation settings by using voice analysis techniques. Such a non-invasive analysis which can easily be integrated into the control software of the stimulation device can improve the usefulness of vagus stimulation significantly.

Appendices

Author Contributions

All authors equally contributed on writing the paper.

Acknowledgments

None declared.

Conflicts

All the aforementioned authors work for Vagustim Bioelectronics.

Ethical Declaration

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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