Differentiation between Migraine without Aura and Chronic Tension-type Headache Based on HOS Analysis of sEMG Signals

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Abstract: *Tension-type headache is the most prevalent form of headache. Nevertheless, the majority of current classification systems for this kind of headache rely on qualitative descriptions and clinical symptoms rather than practical rules, which are less distinct from migraineous features. The aim of this study was to introduce new diagnostic criteria for differentiation between CTTH and migraine patients using nonlinear analysis of surface EMG signals recorded from temporalis muscle. The subjects were eight patients with chronic tension-type headache, ten migraine patients without aura and eight healthy, age and sex matched volunteers. The focus of this study was on HOS analysis and examining the bispectral patterns and extracting features based on entropy concept for differentiation. The results showed that negentropy was the only feature, which could distinguish three studied groups. However, pairwise analysis indicated that NBE was capable of differentiating between migraine and CTTH patients. In addition, bispectral magnitude and specially phase diagrams, enabled us to visually differentiate studied groups.*

Keywords: Chronic tension-type headache (CTTH), diagnosis, higher order statistics (HOS), migraine headache, surface electromyography (sEMG).

1. Introduction

Tension-type headache (TTH) is the most prevalent headache. Almost everyone has experienced TTH during his lifetime [1]. Nevertheless, pathophysiology of TTH is not totally understood. Whether the pain in TTH originates from myofascial tissue or from central mechanisms in the brain is still unsolved [2,3,4,5]. TTH is a “featureless” headache, which means that it is diagnosed mainly by the absence of features found in other types of headache, particularly in migraine [4,6]. However, some patients who are diagnosed as TTH patients, have also clinical features that are usually seen in migraine [6]. Thus a differential diagnosis between TTH and migraine can be difficult [7]. Unfortunately, there are no comprehensive and helpful researches on finding specific diagnostic criteria for TTH [6]. Moreover, the main limitation of current classification systems for headache is that they only rely on qualitative descriptions and clinical symptoms [7]. Chronic TTH (CTTH), occurring on 15 days or more per month, is a major health problem. Regardless of physical suffering, CTTH often impairs individual’s productivity, social time, family dynamics and causes socioeconomic costs [3,6,5]. Because of the limited knowledge of mechanisms leading to this disorder, developing effective treatments is difficult [3].

Though there have been a number of factors associated with CTTH, muscular factors have often been considered as one of the major contributors for CTTH [5]. Therefore, many researchers have used electromyography (EMG) to investigate the possible relationship between pericranial muscle activity and TTH [8]. EMG studies in TTH include evaluation of EMG signals during rest or contractions. In EMG studies published before 1983, about 50% reported normal findings, whereas the other half reported increased EMG activity in TTH patients [8]. In more recent studies, an increased EMG activity in TTH patients compared with controls has been confirmed, but EMG has proved unable to assign individual subjects to specific diagnostic group [8]. This conclusion may result from the fact that all mentioned EMG processing methods are limited to linear ones such as root mean square (RMS), zero crossing (ZC) and median frequency (MDF). However, human body is a complex system and physiological signals are non-stationary, nonlinear and chaotic in nature. Actually, linear and power spectral frequency methods are not very effective in the diagnosis of biosignals [9].

The aim of this study is to introduce new diagnostic criteria for differentiation between CTTH and migraine patients using nonlinear analysis of surface EMG (sEMG) signals recorded from temporalis muscle. Temporalis is a cranial muscle with neural supply, which makes it important in headache investigations. In this work, the focus is on HOS analysis and examining the bispectral patterns and extracting features based on entropy concept for differentiation. These HOS based nonlinear dynamical features which are based on chaos theory, are applied to headache area for the first time in this article.

2. Materials and Methods

2.1 Subjects

Forty six subsequent headache patients were recruited from neurological outpatient clinic at Quaem University Hospital, with thirty one healthy, age and sex matched controls from the hospital staff. The patients were diagnosed according to the criteria of International Classification of Headache Disorders (ICHD- II) [10]. All subjects completed a headache questionnaire and underwent a general physical and neurological examination by two experienced neurologists before entry. A diagnostic headache diary had to be filled out during a six month run-in period to ensure that the subjects fulfill the inclusion criteria and to get some information about the frequency of headaches and the last headache attack. To be included, the headache problem of patients needed to have persisted for longer than six months and age ranged between 20 to 45 years. Criteria for healthy controls were self report of subjects that they had never considered themselves to be a headache sufferer and their headache diary which should contain at most one mild headache per month. The exclusion criteria for both patients and controls included, the daily and continues headache, coexistence of other syndromes such as cluster headache, other neurological, systemic (thyroid disease, hypertension) or psychiatric disorders such as depression, brain MRI positive for the presence of any intracranial pathology, fractures in skull, shoulders and mandible, filled or extracted molar teeth, ingestion of major medications including prophylactics for headache, drug abuse or dependency, presence of postural hypotension, visual acuity below 10/10, pregnancy and cardiac pacemaker.

Of these 77 study participants, for further analysis eight patients with chronic tension-type headache (CTTH), ten migraine patients without aura (MwoA) and eight healthy controls (HC) were chosen.

The measurements were carried out in the Department of Neurology, Mashhad University of Medical Sciences, Mashhad, Iran. All of the recordings were done by the same blinded observer (FA) and between 4-7 PM. Patients were examined when free of headache and neck pain and analgesic and muscle relaxant use 24 hours prior to recording. The demographic characteristics of subjects in three groups are shown in TABLE I.

All subjects received study information form and signed an informed consent prior to their inclusion. The study design was approved by the local Ethical Committee.

2.2 Study Design

Surface EMG activity was measured from left temporalis muscle unilaterally using PowerLab/4SP-SP5638 and dual Bio Amp Stimulator[1] systems. Data were collected during rest, while the subjects were free of headache and neck pain. For the rest state, the subjects were asked to lie in the supine position on the examination bed, both shoulders and thorax against the bed. The knees were adjusted at 60° angle and the hands were straight at both sides of the body [11]. After the adaptation period of one minute, the subjects were asked to close their eyes in order to avoid blink artifacts. Then surface EMG signals were recorded for one minute at rest. Recordings were done bipolarly using Ag/AgCl circular self-adhesive disposable pre-gelled surface electrodes[2] of 15 mm diameter. The position of the electrodes was based on the palpation of muscles during resisted isometric contractions. For temporalis muscle, one electrode was applied just above the zygomatic arch on a line running from the outer canthus of the eye to the upper attachment of the auricle. The second electrode was placed 2 cm above the first one [12]. The reference electrode was placed near the bony area over the medial part of the clavicle (Fig. 1). To keep the interelectrode resistance low, the electrode sites were cleaned with 70% isopropyl alcohol. The leads were fixed by medical type to reduce motion artifacts. The examination was performed in a standardized way by the same observer.

The surface EMG signals were recorded online. A computer was connected to the recording system via USB cable for the storage and display of signals. The raw signals were filtered through hardware lowpass and highpass filters with cut-off frequencies at 500 Hz and 10 Hz, respectively. A notch filter with center frequency at 50 Hz was also used to reduce power line noise. The signals were made discrete using 16-bit analog-to-digital (A/D) converter. According to the mentioned frequency band, the sampling frequency was chosen at 2 kHz. The sampling frequency and recording process (start/stop and the duration of the adaptation and rest stages which lasts one minute for each stage) were controlled through LabChart 7.3 software (ADInstruments Pty Ltd. Australia) which was installed on a computer.

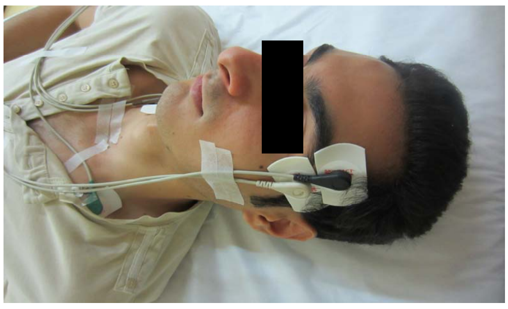

Fig. 1: Bipolar surface electromyographic electrode placement over the temporalis muscle.

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[1] ADInstruments Pty Ltd. Australia.
[2] Ag/AgCl, F55, Skintact, Leonhard Lang GmbH, Austria.

TABLE I: Demographic Characteristics of Subjects.

Group / Variables	CTTH (N=8) Mean (SD)	MwoA (N=10) Mean (SD)	HC (N=8) Mean (SD)	p-value
Age (years)	36.12 (11.43)	31.3 (7.80)	29.75 (4.43)	0.187
Height (cm)	160.37 (6.63)	163.90 (6.70)	164.87 (6.85)	0.405
Weight (kg)	64.37 (11.50)	69.30 (10.18)	67.25 (14.10)	0.760
Body Mass Index (kg/m^2)	24.82 (2.61)	25.80 (3.42)	24.56 (3.51)	0.687
Gender				0.618
Male	0	1	1	
Female	8	9	7	

Kruskal-Wallis test.
Values are mean (standard deviation).
SD, standard deviation; CTTH, chronic tension-type headache; MwoA, migraine without aura; HC, healthy control.

2.3 Bispectral Analysis

For a stationary, discrete, zero mean random process x(n), the higher order spectra (HOS) or polyspectra are defined based on moments or cumulants of order greater than two. The bispectrum is a particular form of HOS, which is defined as the two-dimensional Fourier transform of the third order cumulant [13,14]:

$$B(\omega_1,\omega_2)=\sum_{\tau_1=-\infty}^{+\infty}\sum_{\tau_2=-\infty}^{+\infty}c_3^x(\tau_1,\tau_2)e^{-j(\omega_1\tau_1+\omega_2\tau_2)} \quad (1)$$

The $c^x_3(\tau_1,\tau_2)$ variable reveals the third order cumulant, which is defined as "Equation (2)":

$$c_3^x(\tau_1,\tau_2)=E\{x(n)x(n+\tau_1)x(n+\tau_2)\} \quad (2)$$

Where E[.] denotes the expectation operation. By setting n+ τ_1=m, n+ τ_2=k and substituting "Equation (2)" in "Equation (1)" and splitting the exponent, it can be shown that [9]:

$$B(\omega_1,\omega_2)=E\{X(\omega_1)X(\omega_2)X^*(\omega_1+\omega_2)\} \quad (3)$$

Where X(.) denotes the Fourier transform of x(.). As is evident, we can obviously state that the bispectrum measures the correlation among three frequencies, ω_1, ω_2, (ω_1+ω_2) and estimates the phase coupling [15]. The frequency f ($\omega/2\pi$) may be normalized by sampling frequency to be between 0 and 1. Due to symmetry properties, knowledge of bispectrum in the triangular region $\omega_2\geq0$, $\omega_2\geq \omega_1$, $\omega_1+\omega_2\leq\pi$ is sufficient to describe the rest. This region is shaded in Fig. 2 and labelled by 1 and ensures that there is no bispectral aliasing [9,15]. In contrast with the power spectrum, which is real valued, non negative and a function of one frequency variable, the bispectrum is a function of two frequencies and complex valued, as a result, it has both magnitude and phase.

2.4 Higher Order Statistical Feature Extraction

Although the phase and amplitude plots of bispectrum enable us to visually differentiate physiological or pathological states, it is not practical to use these plots for automatic pattern recognition by computers. Thus, in this study, several features were extracted from higher order cumulants and bispectrum to distinguish healthy, CTTH and Migraine groups based on entropy concept. The feature set consists of entropies in time and frequency domains. Moreover, they are derived either from amplitude or phase of the plots.

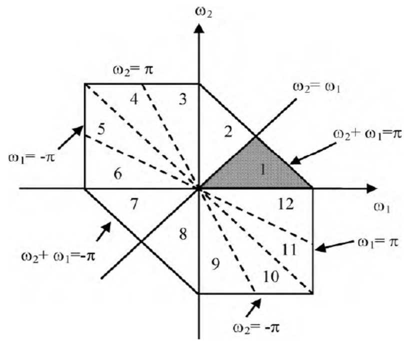

Fig. 2: Symmetry regions of the bispectrum and non-redundant region, which is shaded and labeled by 1.

2.4.1 Amplitude Based Entropies

In this study, three bispectral entropies are derived to characterize the regularity or irregularity of EMG signals in three groups. These features are similar to spectral entropy [16]. "Equations (4-9)", show formulae for these bispectral entropies:

a. *Normalized Bispectral Entropy (NBE)*

$$NBE=-\sum_i p_i\log p_i \quad (4)$$

Where

$$p_i=\frac{|B(f_1,f_2)|}{\sum_\Omega |B(f_1,f_2)|} \quad (5)$$

b. *Normalized Bispectral Squared Entropy (NBSE)*

$$NBSE=-\sum_n p_n\log p_n \quad (6)$$

Where

$$p_n=\frac{|B(f_1,f_2)|^2}{\sum_\Omega |B(f_1,f_2)|^2} \quad (7)$$

c. *Normalized Bispectral Cubed Entropy (NBCE)*

$$NBCE = -\sum_m p_m \log p_m \tag{8}$$

Where

$$p_m = \frac{|B(f_1,f_2)|^3}{\sum_\Omega |B(f_1,f_2)|^3} \tag{9}$$

The mentioned features are calculated within the region (1) defined in Fig. 2, which is equivalent to Ω in the above equations. In addition, the normalization ensures that the entropy is calculated for a parameter which lies between 0 and 1 (as required for probability). As a result, entropies NBE, NBSE, NBCE are also in the same range.

d. Negentropy

Negentropy, J, is based on the information- theoric quantity of differential entropy. Negentropy is zero for a Gaussian process, while it is always nonnegative for other distributions. So, it can be used to measure non-Gaussianity of signals. The classical and simple method for approximating negentropy is based on higher order moments. For a zero mean and unit variance random variable x, J is defined as follows:

$$J(x) \approx \tfrac{1}{12} skew(x)^2 + \tfrac{1}{48} kurt(x)^2 \tag{10}$$

Where E[.] is the expectation operation and skew(x) and kurt(x) are the zero- lag third order and forth order cumulants, respectively [17].

2.4.2 Phase Entropy (PE)

Phase entropy is derived from the phase of the bispectrum and is calculated as "Equation (11)":

$$PE = \sum_n p(\psi_n)\log(\psi_n) \tag{11}$$

$$p(\psi_n) = \tfrac{1}{L}\sum_\Omega l(\varphi(B(f_1,f_2)) \in \psi_n) \tag{12}$$

$$\psi_n = \left\{\varphi \middle| -\pi + \tfrac{2\pi n}{N} \le \varphi \prec -\pi + \tfrac{2\pi(n+1)}{N}\right\}, \quad n = 0,1,\ldots,N-1 \tag{13}$$

Where L is the number of points within the region 1 in Fig. 2, φ is the phase angle of bispectrum, Ω refers to the shaded space in Fig. 2 and l(.) is an indicator function which gives 1, when φ is within the range of bin ψ_n in "Equation (13)" [9,16].

The probability density function of the phase is estimated by computing the histogram of φ, while each bin is set as 5- degree (i.e. N=36). The entropy used in this study is the Shannon entropy [9]. The PE would be zero if the process were harmonic and periodic and predictable. As the process becomes more random, the entropy increases.

2.5 Statistical Analysis

Statistical analyses were performed using PASW Statistics 18.0 for windows (SPSS, Inc., Chicago, IL, USA). Kruskal-Wallis test was used to check if there is a significant difference in extracted features among three groups. Since data were not normally distributed, this nonparametric test was used. In comparing the means of multiple groups, the Kruskal- Wallis is the analogue of one- way ANOVA. In addition, for pairwise analysis we used Mann- Whitney U test to compare the differences in mean values of two groups. P-value less than 0.05 was considered significant.

3. Results

In order to perform analyses, the raw EMG signals were made zero mean. In addition, to provide uniformity, the signals were normalized with respect to the absolute value of their maximum. The bispectrum was estimated using direct method as defined in "Equation (3)", by using Higher Order Spectral Analysis (HOSA) toolbox [18]. This method is similar to the periodogram and is referred to as higher order periodogram [9]. Furthermore, it requires the stationarity assumption. The majority of physiological signals are nonstationary in nature. However, it is generally accepted that sEMG signals recorded during rest and isometric contraction, can be considered stationary during a period less than two seconds. Thus we chose two second period of our data to compute the bispectrum. Then, blocks of 256 samples corresponding to 128ms data with respect to the mentioned sampling frequency with 50% overlap were used to estimate the bispectrum for each volunteer. In this way, we could produce roughly 15 realizations to perform averaging and to satisfy the required smoothness and frequency resolution for our estimation. Hamming window was used as the analysis window.

Bispectrum magnitude and phase plots represented in Fig. 3, are obtained after examining the results for all subjects in each group and are typical for each class. However, it should be noted that since sEMG signals are nonstationary, some segments of recorded signals can give dramatically different results. As can be clearly seen, plots derived from three different classes (healthy, migraine and CTTH) are different in structure and distribution of values. Despite healthy and CTTH magnitude diagrams, which are roughly similar quantitatively and qualitatively, migraineurs show distinct plots. The mean value of maximum amplitude is 0.018 for migraine group, while it is about 0.16 and 0.11 for healthy and CTTH volunteers, respectively. Moreover, the bispectrum is substantially nonzero for a small number of frequencies around the origin (lower frequencies) in these two groups, but migraine plots show multiple peaks which are spread over the bifrequency plane. These peaks indicate the presence of nonlinearity in both healthy and patient time series, specially in migraineurs. Examining the plots, we can clearly see the distinct phase diagrams for three groups. As mentioned before, these plots, specially phase diagrams, enable us to visually differentiate studied groups. However, entropy based feature extraction facilitates automatic machine learning.

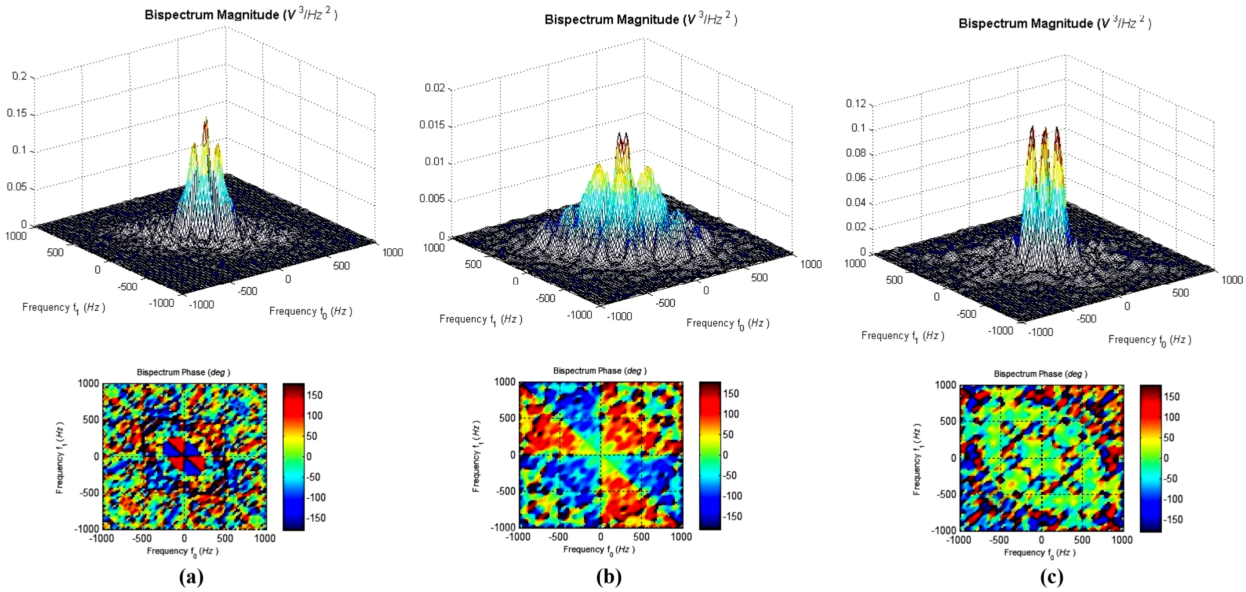

Fig. 3: Magnitude (1st row) and phase (2nd row) of the bispectrum for a HC (a), Migraineur (b) and CTTH patient (c).

TABLE II, represents the results of entropy based features. As is evident, negentropy is the only feature that can differentiate three studied groups. However, pairwise analysis showed that NBE is capable of distinguishing migraine and CTTH. On the other hand, changes in NBSE, NBCE and PE were not significant among groups. Fig. 4, shows the mean variation of negentropy for each group.

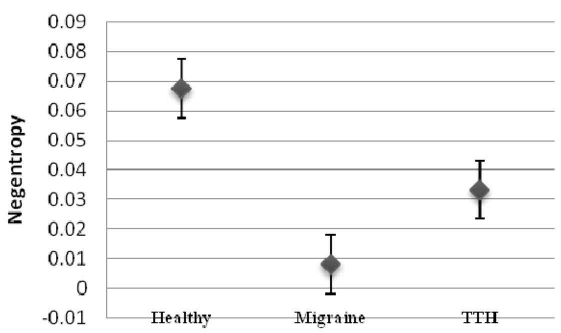

Fig. 4: Mean and standard deviation of negentropy for 3 classes.

4. Discussion

Often myofascial tissue has been assumed to be a crucial source of nociception in TTH [15,19]. Measuring the muscle activity of headache sufferers is, however, not routinely done. In order to help the usability of measuring advice, one objective of the study was to introduce new quantitative diagnostic criteria for TTH capable of differentiating TTH patients from migraineurs and healthy controls.

In order to avoid criteria, which were valuable only during headache attacks and measuring only the nature of headache attack, recordings were done in a headache-free situation. In addition, using non-invasive method (surface electromyography) for assessments, made this diagnostic method easily applicable in clinical practise. Moreover, as methodology was based on HOS analysis, it was firmly consistent with nonlinear and chaotic nature of EMG signals.

Our hypothesis was that there are muscle changes in chronic headache sufferers and these changes persist also between headache attacks. Entropy based features, which were extracted to characterize regularity or irregularity and complexity of EMG signals during headache free periods, reflected more permanent alternations of muscles. As mentioned in section 3, the best discriminant feature between the study groups was the negentropy. This feature shows the temporal and spatial recruitment of motor units which is fundamental for force generation by a muscle and measuring EMG. Since a Gaussian variable has the largest entropy and equivalently minimum negentropy among all random variables of equal variance, the negentropy of almost zero in migraine sufferers indicated that the higher number of motor units are recruited in temporalis muscle of migraineurs during rest and headache free periods when compared to healthy controls. This finding is consistent with previous works which state that during chronification, the muscle load divides in a new way such that painful or deep muscles become week and work less, while superficial muscles become hyperactive [19]. In addition, according to the study group of Nazarpour, probability density function of EMG signals is closer to Laplacian in light force and tends towards Gaussian with increasing force levels, our negentropy results showed altered recruitments of motor units in patients compared to healthy ones during rest[17]. This again confirms the results of Jensen, which showed that temporalis muscles of healthy controls were more relaxed when compared to those of headache sufferers [20]. As expected, the NBSE and NBCE were also maximum in migraine group.

TABLE II: Result of Various Entropy based HOS Features for 3 Classes.

Group / **Features**	HC Mean (SD)	MwoA Mean (SD)	CTTH Mean (SD)	P-value	Pairwise Differences
NBE	0.845 (0.037)	0.845 (0.06)	0.818 (0.03)	0.172	0.048†
NBSE	0.523 (0.112)	0.606 (0.122)	0.565 (0.073)	0.186	NS
NBCE	0.335 (1.736)	0.442 (0.146)	0.416 (0.100)	0.224	NS
J	0.068 (0.07)	0.008 (0.014)	0.033 (0.024)	0.002*	0.002† 0.001□
PE	3.575 (0.008)	3.572 (0.011)	3.574 (0.004)	0.184	NS

Kruskal-Wallis test, Mann- Whitney U test.
Values are mean (standard deviation).
SD, standard deviation; CTTH, chronic tension-type headache; MwoA, migraine without aura; HC, healthy control; NS, non-significant; NBE, normalized bispectral entropy; NBSE, normalized bispectral squared entropy; NBCE, normalized bispectral cubed entropy; PE, phase entropy.
* Significant difference among three groups (p<0.05, Kruskal-Wallis test).
† Significant difference between MwoA and CTTH (p<0.05, Mann- Whitney U test).
□ Significant difference between MwoA and HC (p<0.05, Mann- Whitney U test).

Muscle tenderness has been found in association of different kinds of headache increasing with headache frequency. As spreading of pain has been regarded to be a marker of headache chronification, it could be thought that in a chronification process EMG-findings of TTH and migraine sufferers become similar to each other. In this study population, also in chronic phase of headache, there were distinctive differences between migraine and tension-type headache. It is possible that in a chronification process of tension-type headache and migraine, partly different mechanisms are involved although muscle activity plays a role in both headache types.

As the study population consisted of chronic headache patients with healthy controls, more studies are required to clarify the importance of these EMG –findings in non-frequent headache sufferers in general population. However, the use of quantitative measuring can be of great value in future headache studies and in clinical practise.

In addition to quantitative features, which were a great step forward in facilitating automatic machine learning for future studies, we also introduced potential visual aids for the diagnosis which are fast and easy to use.

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