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Research report

Separating normosmic and anosmic patients based on entropy evaluation of olfactory event-related potentials

C. Güdücü[a,b,*], B.O. Olcay[c], L. Schäfer[b], M. Aziz[b], V.A. Schriever[b], M. Özgören[a], T. Hummel[b]

[a] Dokuz Eylul University Faculty of Medicine Department of Biophysics, 35340 Balcova, Izmir, Turkey
[b] Interdisciplinary Center "Smell and Taste", Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany
[c] Izmir Institute of Technology, Faculty of Engineering, Electrical and Electronics Engineering Department, 35430 Urla, Izmir, Turkey

HIGHLIGHTS

- A novel automated diagnostic tool for anosmia is proposed.
- Entropy based approach to detect chemosensory responses for identifying anosmia.
- This method can guide the clinicians and researchers in chemosensory field.
- Anosmic patients can be correctly (over 75%) diagnosed using this tool.

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ABSTRACT

Objective: Methods based on electroencephalography (EEG) are used to evaluate brain responses to odors which is challenging due to the relatively low signal-to-noise ratio. This is especially difficult in patients with olfactory loss. In the present study, we aim to establish a method to separate functionally anosmic and normosmic individuals by means of recordings of olfactory event-related potentials (OERP) using an automated tool. Therefore, Shannon entropy was adopted to examine the complexity of the averaged electrophysiological responses.
Methods: A total of 102 participants received 60 rose-like odorous stimuli at an inter-stimulus interval of 10 s. Olfactory-related brain activity was investigated within three time-windows of equal length; pre-, during-, and post-stimulus.
Results: Based on entropy analysis, patients were correctly diagnosed for anosmia with a 75% success rate.
Conclusion: This novel approach can be expected to help clinicians to identify patients with anosmia or patients with early symptoms of neurodegenerative disorders.
Significance: There is no automated diagnostic tool for anosmic and normosmic patients using OERP. However, detectability of OERP in patients with functional anosmia has been reported to be in the range of 50%.

1. Introduction

EEG-based brain responsiveness is traditionally evaluated using methods such as temporal averaging and peak measurement of event-related potentials (ERP). Despite the advantages of classical electrophysiological analysis methods, these methods have limitations in some of the sensory modalities, especially in olfaction. One of the biggest limitations in the electrophysiological exploration of olfactory responses is the low signal-to-noise ratio (SNR) due to heterotopic generation of the signal (Boesveldt et al., 2007). Other issues refer to sensory transduction/environmental factors resulting in temporal jitter (Boesveldt et al., 2007; Huart et al., 2012). To overcome these limitations, novel data analyzing methods (e.g. nonlinear data analysis techniques) have been proposed (Guducu et al., 2015; Huart et al., 2013; Lanata et al., 2016; McBride et al., 2013; Olcay, 2014; Quiroga et al., 2001), including entropy analyses (Olcay, 2014, 2017). In theory, entropy is a measure that quantifies the uncertainty of the system behavior (Carhart-Harris et al., 2014; Cover and Thomas, 2006) and has been used in neuroscience to uncover the response characteristics of the brain to internal and external events. For example, Tsallis entropy of the brain activity allows to discriminate healthy people from patients with traumatic brain injuries (TBI) (McBride et al., 2013). Also, visual

* Corresponding author at: Dokuz Eylul University Faculty of Medicine Department of Biophysics, 35340 Balcova, Izmir, Turkey.
E-mail address: cagdas.guducu@deu.edu.tr (C. Güdücü).

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and somatosensory stimulus-induced brain activity has been characterized by means of entropy-based methods (Cao et al., 2017; Olcay et al., 2017). Using the coupling characteristics of the EEG channels yields a rate of 88% activity recognition performance. In one study, 1500 and 1600 Hz auditory stimuli and, in a different study, olfactory stimuli were presented to analyze brain responses using the entropy evaluation of the wavelet energies of the event-related brain signals (Cek et al., 2010; Guducu et al., 2015). Also, olfactory stimuli induce different functional connectivity patterns in Parkinson's disease (Guducu et al., 2015). An additional entropy-based method, so-called mutual information, has been used to capture alterations in the brain connectivity patterns of Alzheimer's Disease (Jeong et al., 2001).

Although there is a relatively large body of literature on olfactory-related brain responses, clinicians still struggle with the diagnosis of olfactory disorders based on electrophysiological recordings. This is especially noted in the discrimination/diagnosis of anosmic and hyposmic patients with special consideration of medico-legal cases. Since olfactory brain responses are not always found in normosmic people due to the low SNR (Gudziol et al., 2006) clinicians are looking for a more precise approach to evaluate the electrophysiological data. There are numerous promising studies that evaluate the response characteristics in the time-frequency domain (Huart et al., 2013; Lanata et al., 2016). One of these studies investigated differences between trigeminal and olfactory stimuli (Huart et al., 2013) while others investigated the pleasantness of odors (Lanata et al., 2016). However, to our knowledge, none of these methods allows to classify the patients with satisfactory precision.

Aim of the current study was to evaluate the smell performance of the participants with or without olfactory loss by utilizing the entropy-based method. The entropy of the averaged signal taken from pre-, during, and post-stimulus frames was calculated for both groups. It is shown that the complexity of the EEG would increase significantly during stimulus processing (Cao et al., 2017). Therefore, it is expected that, during the olfactory stimulation, the complexity of the EEG would increase in normosmic participants, but not in anosmic participants.

2. Results

The entropy values were calculated for all normosmic and anosmic patients. The grand averages of normosmic and anosmic participants are given in Fig. 1. Also, mean entropy scores (E_M) for each time window are given in Table 1. For simplifying the statistical analysis, E_M values before the stimulation (TW1) were assumed to be similar for both groups. Therefore, ΔE_M values for the difference between TW1 and TW2 (ΔE_{M21}), and TW1 and TW3 (ΔE_{M31}) were calculated to show the real change after the stimulus based on that assumption. According to the Rm-ANOVA, there were significant main effects and interactions. First of all, rm-ANOVA showed a significant main effect for group ($F_{1,100} = 4.27$, $p < 0.05$, $\eta_p^2 = 0.041$). Entropy values of the anosmic and normosmic subjects were significantly different. Additionally, rm-ANOVA showed a significant time effect ($F_{1,100} = 21.99$, $p < 0.001$, $\eta_p^2 = 0.18$). ΔE_M values were significantly different between the ΔE_{M21} and ΔE_{M31} within both groups. Apart from these differences, there was also a significant interaction between the factors group and time window ($F_{1,100} = 38.21$, $p < 0.001$, $\eta_p^2 = 0.28$). While there was a significant difference in the normosmic group between the time windows ($p < 0.001$), there were no significant changes in the anosmic group ($p > 0.05$). Also, Rm-ANOVA showed a significant interaction between the factors time window, nostrils and group ($F_{1,100} = 4.96$, $p = 0.028$, $\eta_p^2 = 0.047$). Specifically, there were significant entropy changes between the time windows for both nostrils in the normosmic group (all $p_s < 0.001$), but there were no significant differences in the anosmic group (all $p_s > 0.05$).

Hence, for both sides of stimulation entropy values increased during stimulus processing (TW2-TW1) and decreased after initial stimulus processing (TW3-TW1). Therefore ΔE_{M21} is significantly higher than the ΔE_{M31} in the normosmic group but not in the anosmic group.

Furthermore, we observed that there were significant differences in entropy changes between the groups. Entropy values did not differ during TW1 ($p > 0.05$). In TW2, for both nostrils, the normosmic group exhibited higher entropy values than the anosmic group (for the left and right nostril, $p < 0.001$; see Table 1). For TW3, the anosmic group had higher entropy values than the normosmic group for right nostril stimulation ($p = 0.038$), whereas there was no significant difference for left nostril stimulation ($p > 0.05$). The boxplot demonstration of these values can be found in Fig. 2.

In addition to the statistical analysis, we additionally examined the validity of the proposed method with a classification scheme. Status of olfactory function (i.e. anosmic or normosmic) was tried to be identified by classifying the subjects with regard to the means of the entropy

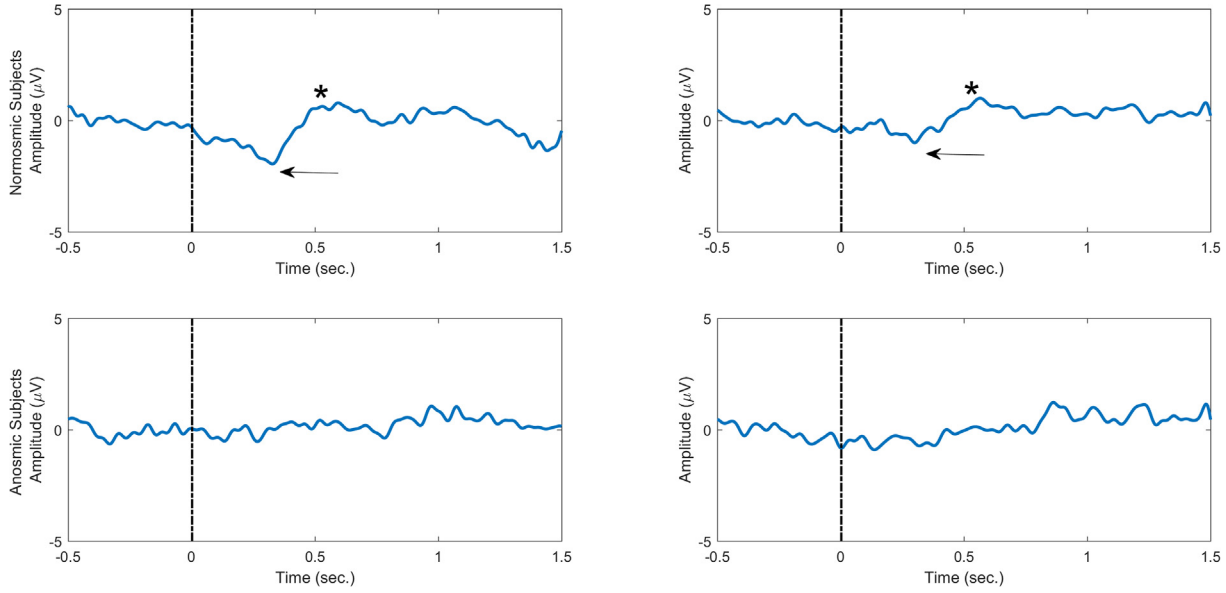

Fig. 1. Grand averages of Olfactory Event-Related Potentials for anosmic (bottom row) and normosmic (top row) participants, separately for the left (left side) and right nostrils (right side). Lines indicate stimulus onset, arrows are pointing at N1 peak, and stars indicate the late positivity. Responses in functionally anosmic patients were delayed and exhibited smaller amplitudes.

Table 1
Mean entropy values (E_M ± standard deviations) for all participants in each time window separately for the two nostrils.

Windows Group	Pre-stimulus (TW1) (−400 to 0 ms)		During-stimulus (TW2) (400–800 ms)		Post-stimulus (TW3) (1100–1500 ms)	
	Left Nostril	Right Nostril	Left Nostril	Right Nostril	Left Nostril	Right Nostril
Anosmic (n = 56)	1.43 (± 0.47)	1.43 (± 0.46)	1.40 (± 0.47)	1.39 (± 0.48)	1.43 (± 0.47)	1.46 (± 0.41)
Normosmic (n = 46)	1.46 (± 0.39)	1.48 (± 0.47)	1.72 (± 0.39)	1.72 (± 0.42)	1.45 (± 0.43)	1.27 (± 0.48)

values obtained from right-sided and left-sided nostril stimulations separately and combined (i.e. each subject was characterized by 3- or 6-dimensional entropy vectors). For classification, Fisher's linear discriminant (FLD) analysis was used. To determine the overall performance, a leave-one-out cross validation strategy was adopted. In this scheme, at each validation step, one of 102 participants' entropy vector were picked out for testing and the classifier was trained with the remaining 101 participants' entropy vectors, and, the 102 individual performances were averaged. Results are presented in a confusion matrix (Table 2); we found that pre-, during-, post- entropy values allow to identify the status of the olfactory function with 83.3% accuracy for the right nostril, 65.7% accuracy for the left nostril and 75.5% accuracy for both nostrils.

We also tried to identify the anosmic and normosmic participants by means of their entropy pattern manually. With the suggested method, participants were correctly diagnosed in 73.5% for the right nostril data and in 72.5% for the left nostril data (Table 3). According to these results, the currently proposed method seems to work slightly better in the classification of the anosmic group than the normosmic one. While the ratio of correct diagnosis for anosmic participants ranged between 77 and 79%, in normosmic participants this figure was 67%.

3. Discussion

In the current study, entropy estimation of distinct portions of averaged EEG activity was used for identification of anosmic and normosmic people based on their OERP recordings.

The electrical activity of the brain has been described as nearly chaotic (Beggs and Timme, 2012). Studies utilizing entropy analysis revealed that the uncertainty in the frequency content of the oscillatory activity of neural structures shifts towards a more ordered state during processing of external stimuli, and returns to its complex nature shortly after the completion of processing of the stimulus (Quiroga et al., 2001; Rosso, 2007; Rosso et al., 2001). To observe the alteration of the entropic behavior of the frequency content, wavelet-based methods are among the most frequently adopted techniques. However, to obtain a reliable entropy evolution, mother wavelet function should be selected properly. Imprecise selection of the wavelet function may not uncover hidden important dynamics embedded in the signal. As an example, the wavelet denoising approach has been widely used to extract stimulus-induced event-related oscillations from single trials activities. In such studies (Ahmadi and Quian Quiroga, 2013; Quiroga and Garcia, 2003), discrete wavelet transform was used to obtain the time-frequency domain energy coefficients. Then, a universal threshold was applied to identify which coefficients on the post-stimulus period belong to stimulus induced brain activity. In such studies, as in wavelet entropy studies, selection of proper wavelet function is of great importance. Apart from that, SNR of the analyzed signal greatly affects the filtering performance.

The data-driven approach called empirical mode decomposition (EMD) decomposes the signal into almost orthogonal basis and adaptive filtering approach which utilizes inherent signal statistics. These approaches were applied to recover the event-related brain potentials from the contaminated EEG activity (Lam et al., 2005; Wu et al., 2012). In the EMD based study, the signal was decomposed into several intrinsic mode functions (IMF) by means of a sifting procedure. Then, by using the averaged activity, the frequency of interest was calculated. Based on these frequency band selections, IMFs were chosen so that their mean frequency coincided with the frequency band of interest. Also, in the adaptive filtering technique, selection of both, the channel for noise cancellation and the proper target for signal enhancement is of great importance.

In this study, we estimated the entropy using the nearest neighborhood statistics of the averaged signals in pre-defined time windows. We found significant entropy enhancement during the stimulus period which is thought to be related to central processing of the chemosensory information. It may be inferred that, during the stimulation period, in addition to background brain processes, the raw chemosensory information is processed in neural ensembles to extract meaningful features for identifying the odor within a specific frequency band. Therefore, it is expected that entropy values return to their original level after processing of this chemosensory information. In the current experimental setup, we used three distinct periods to analyze the pre-stimulus (TW1), stimulus (TW2) and, post-stimulus time windows (TW3) of averaged EEG data. Instead of taking the whole signal for analyzing the entropy change, we decided to analyze segments of equal-length from the recordings. The reason of taking such portions is to avoid the bias of entropy estimation due to the different lengths of the signal. Chemosensory-induced brain potentials arise at around 250–320 ms after the stimulus onset and last about 500–600 ms (Huart et al., 2013). To capture these changes, we restricted the analyzed signal with time-windows taken from three different periods (pre-

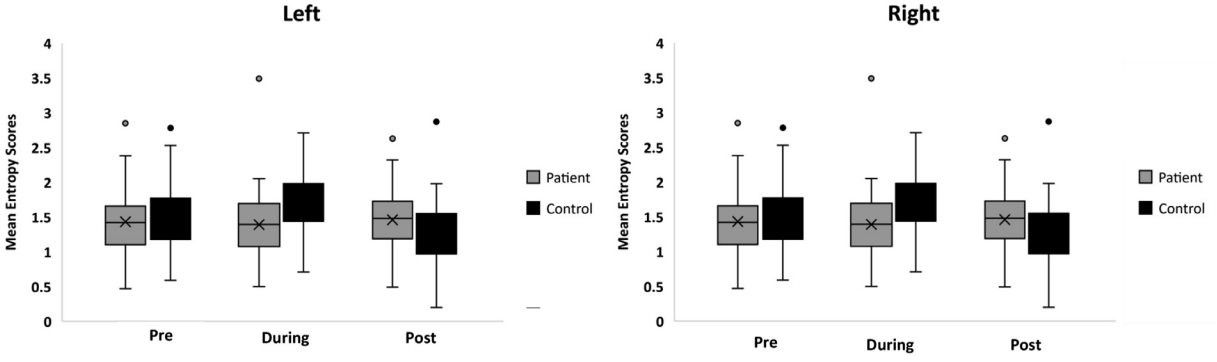

Fig. 2. The boxplot demonstration of entropy values for pre-, during- and, post-stimulus areas in normosmic and anosmic participants.

Table 2
Confusion Matrices (Entropy vector characterized by right, left nostril and both right and left nostrils).

		Estimated					
		Right Nostril		Left Nostril		Both Nostrils	
		Anosmic	Normosmic	Anosmic	Normosmic	Anosmic	Normosmic
Real	Anosmic	49	7	44	12	45	11
	Normosmic	10	36	23	23	14	32
Performance		83.3%		65.7%		75.5%	

stimulus window as −400 to 0 ms, during-stimulus window as 400–800 ms, and post-stimulus window as 1100–1500 ms).

According to the results of the current study, in the normosmic group, entropy values increased during the stimulus (TW2) and decreased after the stimulation (TW3) period again to reach the baseline level before stimulus-onset (TW1). With the additional analysis, it is assumed that the pre-stimulus period of both groups was similar. Analysis revealed significant entropy changes between the During-Pre-stimulus period and the Post-Pre-stimulus period only for the normosmic group.

To our knowledge there are no similar studies aimed to classify olfactory dysfunction patients by means of CSERP (both olfactory and trigeminal event related potentials) related measurements. Until now, entropy has been employed with spontaneous EEG to evaluate the possible differences between patients with TBI and healthy controls during a memory task (McBride et al., 2013). In two different studies, entropy analyses were employed to capture the brain activity in response to auditory (Cek et al., 2010) and somatosensory (Olcay et al., 2017) stimulation in healthy people. Guducu et al. (2015) established differences between healthy subjects and Parkinson's disease (PD) patients. They showed that classical CSERP measurements revealed similar results in both groups. However, there were significant entropy changes between the time windows in the normosmic group but not in the patient group in regard to OERP. In the current study, we also found that the entropy values were significantly changing during the time windows TW1-TW2 and TW2-TW3 in the normosmic but not in the anosmic group.

Anosmic patients could be classified correctly at a rate of 77%, and 68% for the normosmic group, meaning that one out of four patients with anosmia might be misclassified with the manual observations. Furthermore, according to the Fisher's LD classification this rate increased to the 83% for the right nostril. In a previous study, it was proposed that, the probability of detection of an OERP is about 50% when the TDI score is about 22.6 which exceeds the level of functional anosmia (Lötsch and Hummel, 2006). Also, in the same study, nearly 80% of the patients with functional anosmia did not show OERP. The currently proposed method increases the probability of OERP detection by at least 20%. The 73% ratio of correctly identified anosmic patients could inform the diagnostic process especially in medico-legal cases. In combination with other measures including physical examination, psychophysical testing and standardized patient history, results from entropy analyses can be excepted to be a very valuable contribution to the clinical decision.

The current approach can be explored in other groups who have similar olfactory dysfunction but different pathologies. Also, it would be of high interest to investigate hyposmic patients. In conclusion, the present method provides an opportunity to evaluate olfactory event-related potentials in an automated manner which in turn would, for example, enable larger studies across different centers.

4. Materials and methods

4.1. Patients, demographics, and behavioral analysis

A total of 102 participants (age 40.6 ± 18.7 years, 54 male) were recruited. The local ethical committee approved the study (EK251112006; EK115042013). All participants were in good mental and physical health. None of the participants was diagnosed for any form of hormonal, neurological or autoimmune diseases known to significantly interfere with the sense of smell. Participants did not eat or drink anything but water one hour prior to the test. They were also asked not to wear any perfume or scented products before and during testing. A figure of experimental procedure is given on Fig. 3.

At first, the sense of smell was tested psychophysically using the Sniffin' Sticks test battery (Hummel et al., 2007) (Burghart, Wedel, Germany). The battery consists of three sections including olfactory threshold, odor discrimination, and odor identification. The odorants were presented to the participants bi-rhinally by means of felt-tip pens, the so called "Sniffin' Sticks". During presentations of odorants, the pens' tip was placed approximately 2 cm beneath both nostrils. Olfactory thresholds were determined for phenyl-ethyl-alcohol (PEA; a rose-like odor) with 16 stepwise dilutions. When measuring the *thresholds*, the single staircase technique based on a 3-alternative forced-choice task was used. Then, odor *discrimination* was assessed over 16 trials. In each trial, three pens were presented, two containing the same odorant and the other containing the target odorant (3AFC task). Lastly, *odor identification* was evaluated by presenting 16 odors. In this part, each odor was presented with four verbal descriptors in a multiple forced-choice format (three distractors and one target). A total score was calculated by summing up the three test results. A total of 56 functionally anosmic patients (31 male, age 46.8 ± 20.0 years) and 46 normosmic (23 male, age 33.2 ± 13.8 years) individuals were included in the study.

4.2. Stimulus properties, electroencephalography recordings, and analysis

Odorants were delivered with a specifically designed and computer-controlled air-dilution olfactometer (Om6b; Burghart MT, Germany). This device allows to present odors without altering any thermal and mechanic conditions inside the nasal cavity. Patients received a total of 60 phenyl-ethyl-alcohol (PEA; a rose-like odor) stimuli (30 at the right and 30 at the left nostril). The concentration of the odorant was 50%

Table 3
Number of correctly diagnosed participants, separately for group and nostril.

Diagnosed By	Normosmic (n = 46)		Anosmic (n = 56)		Total (n = 102)	
	Left Nostril	Right Nostril	Left Nostril	Right Nostril	Left Nostril	Right Nostril
Entropy Analysis	31	31	43	44	74	75

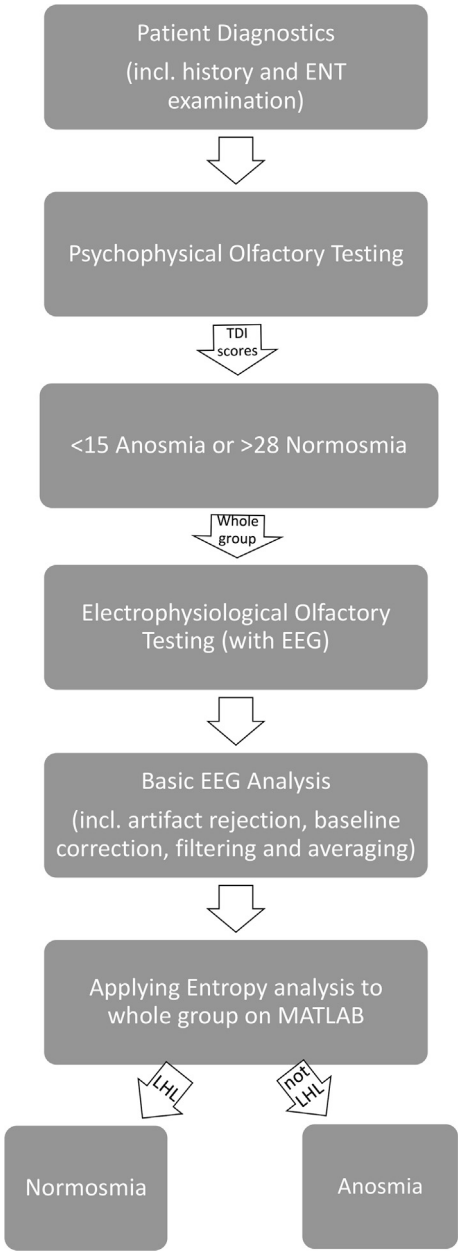

Fig. 3. The block diagram of experimental procedure.

(v/v). The inter-stimulus interval (ISI) was set to 10 s (Whitcroft et al., 2017). During the ISI, only odorless air (control) was delivered. While participants were sitting, and receiving the PEA odorants, the electroencephalogram (EEG) was recorded from 5 locations (Fz, Cz, C3, C4, and Pz, referenced against linked earlobes, A1 + A2) on the scalp with 250 Hz sampling frequency using Ag/AgCl electrodes (Neurofax EEG 8314G amplifier from Nihon Kohden, Rosbach, Germany). Following manual rejection of artifacts (blinks, eye movements, etc.) the signals were applied to a band pass filter (0.5–30 Hz). After the filtering process, all signals were corrected to baseline and averaged in the time domain using Letswave software (http://www.nocions.org/letswave5/). In the chemosensory research area, most of the studies present results from the **Cz** and **Pz** electrodes (Boesveldt et al., 2007). Also, in the clinical settings, these recording positions are widely used. In parallel of the aims of the study, we primarily analyzed the Cz and Pz electrodes to study midline activations. Also, at this level of investigations we were not interested in possible lateralized activations. Therefore, we did not analyze the C3 and C4 electrodes. Also, the **Fz** electrode was discarded due to frequent muscular and blinking artifacts. The entropy estimation was applied to the averaged data using MATLAB (The MathWorks Inc, 2007). Details of entropy analysis are given below.

4.3. Estimating the entropy and selection of time windows

Calculation of the entropy requires the probability density function (pdf) information of the corresponding signal. However, obtaining the marginal pdf from a finite number of samples is not straightforward. A common approach to estimate the pdf is partitioning the histogram into equal-sized/adaptively-sized bins. Alternatively, kernel-based density estimation techniques have been widely used (Principe, 2010). Calculating distribution entropies of reconstructed state-space embedding vectors is another entropy estimation technique (Li et al., 2015). Approximate entropy (Pincus, 1991) and Sample entropy (Richman and Moorman, 2000) are some other approaches to quantify the complexity of the observed signals. Unfortunately, these techniques do not provide an accurate entropy estimation (Kraskov et al., 2004; Wibral et al., 2014). In this study, we have employed an estimation technique that uses the nearest neighborhood statistics of signal samples.

Suppose that X is a continuously distributed random variable. The entropy of the random variable X is defined as (Shannon and Weaver, 1949),

$$H(X) = -\int_{-\infty}^{\infty} f_X(x)\log f_X(x)dx \tag{1}$$

where $f_X(x)$ is the marginal probability density function (pdf) of the random variable X. To estimate the entropy from a limited number of observations, Kozachenko and Leonenko (1987) proposed a novel method given as,

$$\widehat{H}(X) = -\psi(k) + \psi(N) + \log(c_d) + \frac{d}{N}\sum_{j=1}^{N} \epsilon(j) \tag{2}$$

where $\psi(.)$ is the digamma function, k is the number of neighbors, N denotes the sample size of the signal, d represents the dimension of the signal, the volume of d-dimensional unit ball is denoted by c_d, and finally $\epsilon(j)$ represents twice the distance between the j^{th} sample and its k-nearest neighbor. Detailed criteria for the selection of the k parameter are currently lacking. In a study which carries out a performance comparison of different mutual information estimators, Khan et al. (2007) used "kNN-based" mutual information estimation method, and they showed that $k = 3$ yielded more accurate mutual information estimates. Therefore, we selected k as 3 in the current study as well. For this entropy approximation, we calculated the Euclidean distance between signal samples.

Three different time windows were selected as follows: pre-stimulus window (−400 to 0 ms), during-stimulus window (400–800 ms), and post-stimulus window (1100–1500 ms). This selection procedure of the time windows was made according to the temporal pattern of the classical ERP (Kobal and Hummel, 2001). To prevent bias, the lengths of the time windows were equalized. For each time window, entropy values were calculated for Cz and Pz electrodes. Then entropy values in both electrodes were averaged for each time window to investigate changes separately for the pre-processing, during-processing and, after-processing period. It is assumed that during normal olfactory processing, entropy levels of the brain should appear in a low entropy-high entropy-low entropy (LHL) pattern. Since periods of high information (stimulus) processing the brain behaves in a more complex manner, its entropy in during stimulus window is expected to be higher compared to the pre- and post-stimulus periods. Therefore, the LHL pattern was searched for the evaluation of the smell performance of the participants. Participants exhibiting the LHL entropy pattern were diagnosed as having olfactory function (normosmic); participants who did not exhibit the LHL pattern were diagnosed as functionally anosmic.

4.4. Data analysis

For statistical analysis, the SPSS program package was employed (vs. 21; SPSS Inc, Chicago, Ill, USA). To evaluate the possible differences between and within the two groups regarding the three-time windows for both nostrils, repeated measures ANOVA was employed with time windows (During-prestimulus and post-prestimulus time windows) and nostril (right and left) as within-subject factors and group (anosmic and normosmic) as between subject factor. Multiple comparisons were adjusted according to Bonferroni and the level of significance was set to 0.05. Additionally, to validate the method we employed Fisher's linear discriminant classifier for the cluster analysis.

In general, Fisher's linear discriminant classifier finds a linear projection w that can separate two different kinds of pattern vectors in lower dimensional space with minimum error. This projection vector minimizes the intra-class scattering and maximizes the inter-class scattering (Fisher, 1936).

The FLD classifier is formulated as,

$$f(x) = sign(w_{opt}^{T} x + w_0) \tag{3}$$

where w denotes the projection vector that maximizes the criterion function $J(w)$

$$J(w) = \frac{w^T S_B w}{w^T S_w w} \tag{4}$$

In above formulation, S_B and S_W denotes the inter-class and intra-class scatter matrices respectively. The optimum projection w_{opt} vector is calculated using

$$w_{opt} = (\Sigma_{anosmic} + \Sigma_{normosmic})^{-1}(\mu_{anosmic} - \mu_{normosmic}) \tag{5}$$

where $\Sigma_{anosmic}$ and $\Sigma_{normosmic}$ denote the covariance matrices calculated using anosmic and normosmic subjects' entropy vectors, $\mu_{anosmic}$ and $\mu_{normosmic}$ are the mean entropy vectors of both normosmic and anosmic subjects. The w_0 denotes the bias term which was calculated so that it minimizes the error rate on the training set.

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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