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EEG response to different odors in healthy individuals: a promising tool for objective assessment of olfactory disorders

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Abstract

The aim of the present study was to examine human CNS response to three different types of odor: lemon, vanilla and peppermint. Electrophysiological activity was recorded in the baseline state and for three odors, lemon, peppermint and vanilla in 16 healthy participants. For further analysis, electrodes were separated into groups according to the spatial position on the head. Fast Fourier Transformation analysis was performed on every set and mean value of activity in theta interval was exported. As the theta region showed statistically significant results, further analysis was based only on the theta frequency band. On electrodes FP1, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO9 and PO10 there was statistically significant difference in the electrical activity of the brain between four conditions. For peppermint and lemon there was statistically significant difference in activity between different regions ((F (1.576, 23.637) = 16.030, p = 0.000) and (F (1.362, 20.425) = 4.54, $p = 0.035$), respectively), where the activity in the central area was significantly reduced compared to the activity in the other four areas and in the left and right anterior and left posterior area, respectively. There was no statistically significant difference for vanilla in activity between specific areas (F(1.217, 18.257) = 1.155, $p = 0.309$). The results obtained in this study indicate that olfactory stimuli can affect the frequency characteristics of the electrical activity of the brain.

Key words: odor, EEG response, theta band

Introduction

Although many studies have shown that olfactory function is affected in many neurological diseases, olfactory disorders are often neglected in neurological examination and even rarer rated in the clinical setting. Nevertheless, their evaluation can be useful for diagnosis of many neurological disorders like Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease and motor neuron disease. (1) In all of these disorders, basic ability of sense of odors can be reduced, as well as the ability to distinguish different odors or determining thresholds / odor detection. The malfunctioning of the olfactory system can also be an indicator of disease progression and correlate with cognitive deterioration in patients with dementia. (2) According to the results of the meta-analysis, the ability to sense and distinguishing odors could be used as one method of detecting patients with Alzheimer's disease, and the method that examines the threshold stimulus for certain odors could be used in the detection of patients with Parkinson's disease. (3) In patients with mild cognitive impairment (MCI) it was observed that weakened olfactory function, and unconsciousness of the deficit, could also be one of the indicators of progression of mild cognitive impairment to Alzheimer's disease.(4) It is important to mention that the attenuation of function of the olfactory system is also observed during natural aging. (5)

Methods used in the examination of the olfactory system are psychophysical tests, olfactory evoked potentials and functional magnetic resonance imaging (fMRI). The mostly used psychophysical tests are: the University of Pennsylvania Smell Identification Test (UPSIT or SIT) , Connecticut Chemosensory Clinical Research Center Test (CCCRC test) and Sniffin' Sticks test.(1) UPSIT test consists of 40 different scents and is one of the most commonly used tests to determine the functional state of the olfactory system. CCCRC test consists of ten different scents, of which seven are used to test the olfactory system, while three fragrances are used for testing the trigeminal system. Sniffin' Sticks test has three levels and is

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used to test thresholds for different odors, the ability of sense of odors and ability to distinguish between different odors. Lack of psychophysical tests is their dependence on the active participation of patients and their subjective impact. Olfactory evoked potentials are responses of the olfactory system related to specific olfactory stimulus. Their advantage is the independence of the cooperation of participants and the ability to use in situations in which the active cooperation is very difficult to implement. The disadvantage of this method is the need for very precise synchronization of olfactory stimulus with electrical brain activity that has been recorded in a given moment and a need for a complete ventilation of the chamber after each presentation of stimuli, so that each stimulus presentation has the same initial, i.e. neutral conditions as the previous presentation. fMRI on the other hand gives an insight into the functional neuroanatomy of the olfactory system.(1,6-8)

On the other hand several studies have shown that electrical brain activity (electroencephalography – EEG) in humans can be influenced by various odors. (9-12) Despite these promising results, the widespread use and adoption of the method is still missing.

Recording of the electrical brain activity (EEG) is a noninvasive method that could serve as an objective method for evaluating the function of the olfactory system. The method is available in almost every clinical facility, and it is possible to achieve results in a relative short period of time and the method does not require active cooperation of participants. The aim of the present study was to examine human CNS response to three different types of odor: lemon, vanilla and peppermint.

Materials and methods

Sixteen healthy participants participated in this study, 7 females and 9 males (mean age 29+/- 3). They had no known neurological disorders, and according to subjective claims they all have functional sense of smell. Participants were informed about all aspects of the study and

they all signed informed consent approved by Ethical Committee of University Hospital Center Zagreb.

Ability to distinguish odors was determined using a simple test in which participants had to recognize different odors that will be used later in the study. Each odor was presented twice in arbitrary order. All participants recognized presented odors with complete accuracy. During the experiment participants were placed in sound- and light-insulated chamber with its own ventilation system. They sat in a comfortable armchair and were instructed to relax and to minimize blinking in order to reduce internal artifacts. During the experiment participants had to keep their eyes open in order to avoid unwanted alpha activity, which has very large amplitude and occurs in a state in which a person is at rest with eyes closed. Due to the very small amplitude of the signal that is important for this study, the presence of alpha rhythm would mean an unwanted noise. The activity of the alpha rhythm has frequency of 10 Hz, and is better to avoid this activity during the recording of the experiment, so after, during signal analysis, no important parts of signal would be removed with filtering. Participants were asked to minimize their cognitive activity in order to put their brain in "idling" state. Electrophysiological activity was recorded with EEG cap with 31 active electrodes [BrainProducts GmbH, Germany] positioned according to International 10-20 System. Active electrodes based on quality Ag/AgCl sensors have integrated circuits for noise reduction. For further analysis, electrodes were separated into groups according to the spatial position on the head: left anterior - LA (FP1, F3, F7, Fc1, Fc5, T7, C3), right anterior - RA (FP2, F4, F8, FC2, FC6, T8 C4), central - C (Fz, Cz, Pz), left posterior - LP (TP9, CP1, CP5, P3, P7, O1, PO9), right posterior - RP (TP10, CP2, CP6, P4, P8, O2, PO10) as presented in Figure 1. Areas under each electrode were cleaned with abrasive paste in order to reduce impedance and conductive paste was applied to each area in order to achieve adequate conductivity for recording very small signal (order of magnitude $\neg\mu V$). Vertical oculogram was recorded

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below the right eye to detect vertical ocular movements for more precise treatment of ocular artifacts.

Recordings were performed with BrainAmp amplifier and recording software Brain Vision Recorder [BrainProducts GmbH, Germany]. The recording scheme is presented on Figure 2. Recorded signals were filtered with band pass filter from 0.1 Hz to 250 Hz. Sampling frequency was 1000 Hz. Data analysis was performed with software Brain Vision Analyzer [BrainProducts GmbH, Germany].

Each session consisted of five sets, two baseline sets with no odor, and three sets with three different odors (lemon, vanilla, peppermint). During recording, the subject was instructed to breathe evenly through the nose. In the first two sets of recordings no odors were presented to participants; goal of the first set was the preparation for the experiment, so participants could relax and get used to the conditions in the chamber, while in the second set the basic, spontaneous electrical activity of the brain was recorded, and that activity was later used as the basis for comparison with the electrical activity of the brain in experimental conditions. Each participant was his own control, comparing the conditions of spontaneous brain activity with conditions in which the participant was influenced with presented olfactory stimulus. After the initial phase, three different odors in random order were presented to each participant. Odors used in this study were essential oils, recognized by each participant in the initial part of the experiment. Essential oils used in this study were lemon, vanilla and peppermint and were selected according to previously conducted studies. (10,11) Odors were prepared immediately before each set of recordings and presented on clean, unused perfume test strips fixed 10 cm in front of the participant's nose.

Each set, the baseline set and the odor set, lasted two minutes. Between each set there was two minutes break with ventilation system on in order to reduce influence of previously presented odor to odor that will be presented in the next set.

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For each set of data (basic activity, lemon, vanilla, peppermint) a fast Fourier transform (FFT) was performed in order to achieve the separation of the frequency components that are of interest for further analysis. The frequency resolution used in this analysis was 0.002 Hz. The result of the frequency analysis is expressed as a power, i.e. squared amplitude value of activity (μV^2) . Hanning window is used in analysis, in order to reduce the boundary conditions. Mean activity in a particular frequency band was used for further statistical analysis.

Statistical analysis was performed using software IBM SPSS 20.0 (Chicago, IL). The collected data had a normal distribution and was mutually dependent, because there are several successive measurements at the same participant, and suitable statistical analysis was repeated measures ANOVA, with Bonferroni correction for post hoc analysis. P values less than 0.05 were considered statistically significant.

Results

All EEG results were interpreted by regarding each subject as his/her own control (comparison of conditions in which there is an olfactory stimulus with the condition in which there is only a basic activity). The initial analysis was conducted in all frequency bands (alpha, beta, delta, theta) (Table 1), but only the theta region showed statistically significant results and therefore further analysis was based only on the theta frequency band. In the first step of the analysis, we examined whether on each electrode there is a difference between the four conditions (peppermint, lemon, vanilla, basic activity). The analysis was conducted by repeated measures ANOVA. When the rule of sphericity was violated, the Greenhouse-Geisser correction was conducted. The analysis showed that on electrodes FP1, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO9 and PO10 there was statistically significant difference in the electrical activity of the brain between four conditions. Results of the analysis are presented in Table 2. After the initial statistical analysis, post hoc analysis with Bonferroni correction was performed in order to determine exactly between which pairs of conditions there is a statistically significant difference. The results of this analysis are shown in Table 3. In all cases the mean intensity of the electrical activity in the theta band excited with presented olfactory stimulus (lemon, peppermint, and vanilla) was reduced relative to the mean intensity value of primary, spontaneous brain activity. The table shows that the electrical activity of the brain induced with the odor of lemon showed a statistically significant reduction in relation to the baseline spontaneous brain activity on the greatest number of electrodes (15 of 31, 48%), followed by brain activity induced with the odor of peppermint (10 of 31, 32%) and the fewest number of electrodes was activated with the odor of vanilla (3 of 31, 10%). In the second part of analysis, the values obtained at specific electrodes are grouped according to the spatial position in one of the five areas (LA, DA, C, LP, DP) and mean activity value was averaged for each region for each of the three scents (peppermint, vanilla, lemon). For each of the odors, repeated measures ANOVA with Greenhouse-Geisser correction was performed in order to examine whether there was a difference in activity between different areas.

To determine between which areas there was a statistically significant difference, the post hoc analysis with Bonferroni correction was performed, and the results are presented in Table 4. For peppermint there was statistically significant difference in activity between different regions (F (1.576, 23.637) = 16.030, $p = 0.000$), where the activity in the central area was significantly reduced compared to the activity in the other four areas.

There was no statistically significant difference for vanilla in activity between specific areas $(F(1.217, 18.257) = 1.155, p = 0.309)$.

For lemon there was statistically significant difference in activity between different regions (F $(1.362, 20.425) = 4.54$, $p = 0.035$), where the activity in the central area was significantly reduced compared to the activity in the left and right anterior and left posterior area. Figure 3 presents the spatial distribution of mean values of the electrical activity of the brain for peppermint, vanilla and lemon.

Discussion

This study has shown that stimulation with selected odors is associated with a significant reduction in theta band. Furthermore we have shown that lemon and peppermint beside reduction of theta band have the most pronounced effect of the reduction of theta band in the central region (electrodes).

However, it has to be emphasized that previously published studies related to the impact of olfactory stimulus to changes in the intensity of the brain electrical activity were performed with different methodologies. According to some authors, there is a statistically significant difference in the alpha frequency range between conditions in which there is olfactory stimulus and the baseline condition with no stimulus. (13,14) Other studies report a statistically significant difference in the theta frequency range. (9,10,11) The methodology used in the present study was based on the methodology described in the paper by Neil Martin, (11) and the results obtained are consistent with the results obtained in that study, indicating the reproducibility of the results when using a similar methodology. The analysis showed that on electrodes FP1, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO9 and PO10 there was statistically significant difference in the theta electrical activity of the brain induced with odors of peppermint, vanilla and lemon and between the baseline activity. Between activities induced by different olfactory stimulus, there was no statistically significant difference. For all statistically significant

results, the intensity of activity in the theta frequency range induced by certain odor was reduced in comparison with the intensity of activity in the theta frequency range in situations where there was no olfactory stimulus. These results indicate that there is a difference in the electrical activity of the brain evoked by olfactory stimulation related to the baseline electrical brain activity with no presentation of odors.

Lemon and peppermint elicited reduction of intensity of theta activity on larger number of electrodes than vanilla. In initial tests, where participants had to recognize presented odors, most participants characterized scent of vanilla as very mild odor, although it was dosed in the same amount as the other two scents. It is possible that in the case of vanilla arousal of the olfactory system was not the same as the arousal for lemon and peppermint, which is why the influence of the vanilla odor to intensity of brain activity is reduced.

Analysis of the activities of groups of electrodes showed that peppermint and lemon elicited statistically significant difference in the intensity of activity between different regions, while with the odor of vanilla, this difference was not statistically proven. If we compare this with previously presented results where the vanilla had the slightest impact on the intensity of activity of theta band and the fact that the subjects who participated in the survey characterized vanilla as very mild odor, then we can assume that the odor of vanilla did not have the same effect on olfactory system as the other two odors. All odors that were used in this study were rated by participants as pleasant, which is extremely important because the degree of pleasantness is an important factor that has influence on the intensity of activity, and it is also possible to perform a classification of EEG signals to determine whether the odor is pleasant or unpleasant smell for subjects. (15)

For odors of lemon and peppermint, induced activity in the central area was significantly reduced in comparison to the induced activity in the remaining areas. In a study by Cherninskii et al, the changes of activity in given frequency bands were mostly pronounced in

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the left temporal and parietal regions. (16) Also, there was a clear difference between the excitation of the olfactory and trigeminal systems, where the response to trigeminal stimulation (CO_2) occurs in areas of the cortex associated with locomotion of sniffing / smelling, while the response to olfactory stimuli (H_2S) occurs to a greater extent in the primary olfactory cortex. (17) Also, activation of the olfactory area is manifested as increased intensity of the electrode Pz (parietal area), while the activation of the trigeminal nerve is manifested as increased intensity of the electrode Cz (central area). (18)

The amygdala is also a part of olfactory system and its role in emotions and memory gives a complexity to functioning of olfactory system and may be one possible explanation for the different frequency and spatial distribution of research results related to the olfactory system. (15)

Conclusion

The results obtained in this study indicate that olfactory stimuli can affect the frequency characteristics of the electrical activity of the brain. The method itself is non-invasive and easily enforceable and shows promising contribution in testing the functionality of the olfactory system in humans. It is necessary to conduct research on a larger number of participants and in conditions were not only healthy participants are included, but also participants with various neurological diseases.

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Tables

Table 1. A) Results of repeated measures ANOVA that show on which electrodes there was a statistically significant difference between alpha activity in condition with olfactory stimulation and baseline activity

B) Results of repeated measures ANOVA that show on which electrodes there was a statistically significant difference between beta activity in condition with olfactory stimulation and baseline activity.

C) Results of repeated measures ANOVA that show on which electrodes there was a statistically significant difference between delta activity in condition with olfactory stimulation and baseline activity.

Table 2. Results of repeated measures ANOVA that show on which electrodes there was a statistically significant difference between theta activity in condition with olfactory stimulation and baseline activity.

Table 3. Results of repeated measures ANOVA after Bonferroni correction; a statistically significant difference between odors and baseline; comparison of mean values of the activity $[\mu V^2]$

Table 4. Results of repeated measures ANOVA after Bonferroni correction; a statistically significant difference between different areas; comparison of mean values of the activity $[\mu V^2]$

R - Right, L - left, C - central, A - anterior, P - posterior

Figures

Figure 2. Recording scheme.

Figure 3. Spatial distribution of mean values of the electrical activity of the brain for peppermint (A). vanilla (B) and lemon (C).

