



Persistent odors induce hedonic valence-independent alpha and beta wave EEG desynchronization

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ABSTRACT

While electrophysiological responses to olfactory stimulations are widely investigated using electroencephalography (EEG), studies on odor perception often yield inconsistent results. In this work, both early and late olfactory event-related potentials (ERPs) from fifteen healthy participants during sustained presentation of odors were investigated. A custom-designed olfactory stimulation system synchronized with a high-density EEG was used to deliver pleasant, unpleasant and neutral odors during an eyes-closed, non-sniff-locked olfactory stimulation protocol. Both pleasant and unpleasant conditions elicited heightened early ERP amplitudes, compared to the neutral odor, with N40 peaks localized in the occipital region. Presenting the olfactory stimulus continuously for 6 s significantly reduced late ERP global field power, revealing prolonged and spread cortical desynchronizations, particularly in the frontal, central and parietal regions, and especially in the alpha and beta bands. This occurred for both the non-neutral stimulation conditions (pleasant and unpleasant), relative to the neutral one, regardless of their hedonic valence. These findings indicate that cortical responses to olfactory stimuli are manifested by initial occipital sensory gating, followed by persistent and widespread alpha/beta desynchronizations, independently of odor valence.

1. Introduction

Electrophysiological responses to olfactory stimulation are widely investigated via electroencephalography (EEG), primarily through event-related potentials (ERPs) [1–3]. However, using ERPs to understand how the brain encodes and processes olfactory stimuli remains a longstanding challenge. One key limitation arises from confounding factors due to odor sniffing. Indeed, it introduces into recorded signals non-sensory artifacts, due to both the motor activity of inhalation and the cognitive engagement required for odor evaluation, contributing to inconsistencies across studies.

Previous EEG investigations have revealed a variety of frequency components and topographical patterns associated with odor detection. For instance, some studies identified beta and gamma oscillations in the amygdala during odor sniffing, with beta activity synchronized with inspiration [4,5]. Similar beta oscillations were observed between inspiration and exhalation, with amplitudes correlated to stimulus intensity [6]. Invasive local field potentials studies reported evidence of theta and gamma

oscillations in the piriform cortex being responsible for stimulus maintenance (i.e., piriform-hippocampal theta-phase synchrony) and encoding, respectively [7,8]. In particular, a specific temporal sequence was described in the piriform cortex during odor perception: theta oscillations were reported to emerge upon inspiration and quickly diminish, followed by beta and gamma activity [5,7]. Notably, theta waves were also found to appear during clean-air inhalation, suggesting a link with respiratory motor activity rather than odor content [8–10].

Beta and alpha waves are the most frequently reported in olfactory EEG studies [4,11–13]. For instance, a recent study by Amancharla et al. showed that aromatherapy sessions led to increased alpha power and decreased beta power [14]. Similarly, Chow et al. found that lavender odor reduced beta activity in left frontal and central regions, along with gamma activity in the right parietal area [15]. Kang et al. reported alpha power increases in response to acacia perfume and decreases with butanol, relative to a no-odor condition [11]. Other studies noted that pleasant stimuli can increase both theta and alpha activity, particularly in the right prefrontal region [12,16,17].

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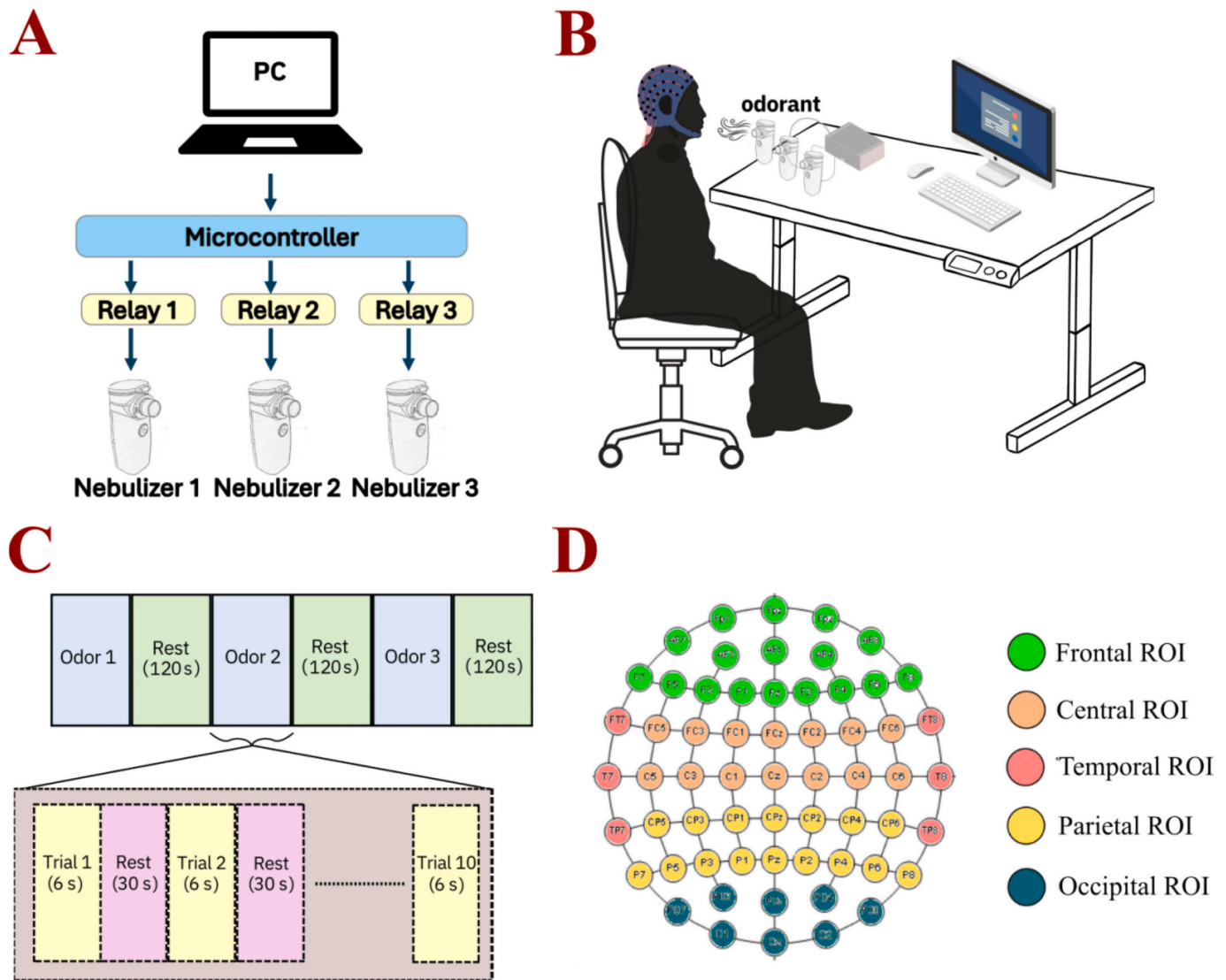


Fig. 1. Experimental setup and olfactory stimulation protocol: A) diagram of the olfactory stimulation system, consisting of three nebulizers, three relays and a microcontroller; B) drawing of the test setup; C) stimulation protocol, showing the timing of the consecutive phases of odor release and resting; D) positions of the recording electrodes, according to the international 10–20 system and grouped by Region of Interests (ROIs).

In this work, we aimed to investigate whether possible differences in olfactory EEG responses could be detected in response to three odors differing in hedonic valence (unpleasant, pleasant and neutral), by examining both early and late ERP components. While early negative ERP components have been linked to olfactory sensory thresholds and odor identification, later positive components are often associated with cognitive processing of odors, particularly evaluation and classification, according to familiarity, pleasantness, and significance [16,18,19].

Odorants were administered by paying attention to minimize the risk of artifacts introduced by sniffing and by visual cues, to isolate odor-driven neural processes. In particular, we sought to clarify the cortical signature of sustained, non-sniff-locked olfactory processing under eyes-closed, no-task conditions that eliminated visual confounds. Specifically, we aimed to characterize whether a continuous odor intake is accompanied by reductions in the ERP absolute power and global field power during stimulation, consistently with sustained cortical processing. Furthermore, by capturing the interplay between rapid, event-locked early responses and subsequent ongoing cortical oscillatory activity, we investigated whether the odor hedonic valence can shape neural interactions during olfactory information encoding. By articulating

these features within a single protocol, our goal was to provide a conservative, reproducible scalp-level readout of ongoing olfactory processing that can inform future basic and translational applications where prolonged stimulations may be needed.

2. Materials and methods

2.1. Odorants and olfactory stimulation system

The investigation was performed using three odorants, classified as unpleasant, pleasant and neutral. The unpleasant odorant was a sulfurous salt-bromine-iodine thermal water (Acqua di Sirmione, Menarini, Italy), having a sulfur smell, resembling rotten eggs. The pleasant odorant was an orange essential oil (*Citrus arantium* L., Oligea Srl, Italy). Both odorants were used without any dilution. The neutral odorant was mineral water. The a priori valence classification was guided by established hedonic ratings, as sulfurous/thiol compounds are typically judged strongly unpleasant, whereas citrus/limonene-rich odors are judged pleasant [20–22]. Moreover, the valence classification was also confirmed by a prior study from our group using the same

set of odorants, in which participants provided ratings showing pairwise significant differences among all three categories (unpleasant vs neutral; pleasant vs neutral; unpleasant vs pleasant) [23].

The odors generated by the three odorants were administered using a custom-made olfactory stimulation system, consisting of three independent mesh nebulizers and a microcontroller, as shown in Fig. 1A. Each nebulizer (Gima S.p.A., Italy) was activated by a relay (KF-301, AZ Delivery, Germany), which was driven by a microcontroller (Arduino Micro, Arduino, Italy). The three nebulizers could be activated according to any desired sequence, by means of a custom script on the microcontroller, combined with a MATLAB custom script. Synchronization between the nebulizers' activation and EEG signal acquisition was achieved using the electroencephalograph's MK channel, which received a trigger signal from the microcontroller.

It is worth pointing out that, as each odorant was administered with its native liquid medium, the stimulation conditions differed not only in odor but also in liquid vehicle. This procedural choice was motivated by ecological validity and by the intention to preserve the characteristic percept of each odorant.

2.2. Olfactory stimulation protocol and EEG data collection

Prior to starting the tests, the subjects were asked to blow their nose, sit comfortably on a chair and relax, to minimize motion artifacts. The nebulizers were positioned ~10 cm away from the subject's nostrils (Fig. 1B). The subjects were instructed to maintain, during the test, their eyes closed and to focus on the presented odor, while breathing naturally, without sniffing the odor.

Each odor was presented with a stimulation train, consisting of a sequence of 10 consecutive stimulations lasting 6 s each. The odor presentation order was randomly selected for each subject. To avoid after-effects in the EEG recordings, any two consecutive stimulations with the same odor were separated by an inter-stimulus rest phase (no odor provided) lasting 30 s. After the completion of the 10 stimulations with the same odor, the subject was given a break of 120 s. The protocol's timing is represented in Fig. 1C.

EEG data were collected using a commercial electrocardiograph (Gal NT, EBNeuro, Florence, Italy) with a 64-channel EEG pre-wired cap, placed according to the international 10–20 system (Fig. 1D). Signals were recorded with a sampling rate of 512 Hz, following the verification that the electrode impedance did not exceed 5 k Ω .

2.3. Participants

The required sample size (number of participants, N) was estimated using a statistical power analysis conducted in GPower (version 3.1; Heinrich-Heine-Universität Düsseldorf, Germany). Assuming a paired-samples t -test, a significance level $\alpha = 0.05$, and a statistical power of 0.80, the expected effect size was derived from the most comparable olfactory EEG studies identified in the literature [24,25]. These studies yielded estimated sample sizes of 7 and 14, respectively. Based on these estimates, and to ensure adequate statistical power, the target sample size for the present study was set at $N = 15$.

Therefore, fifteen healthy adult volunteers (10 females, median age 27 [InterQuartile Range, IQR = 3]), with no major depressive disorders nor a history of previous neurological lesions, were recruited and tested with the three olfactory stimulation trains.

The investigation was performed in accordance with the Declaration of Helsinki and was approved by Ethics Commission of the University of Florence. All participants provided written informed consent to participate in this study.

2.4. EEG signal processing

Each recording was visually inspected for excessive movement noise, before re-referencing unipolar recordings to the grand average, and

high-pass filtered using the MNE library [26]. In particular, a zero-phase filter with a Hamming's window was applied to band-pass only the signal components having frequencies between 1 and 30 Hz, as suggested by the PREprocessing Pipeline (PREP) [27]. Notch filtering (50 Hz) was then applied to further remove powerline interference. Channels with still excessive or uncorrelated noise were labeled following PREP criteria and interpolated by means of spherical spline interpolation [28], using the MNE library. To remove artifacts prior to signal reconstruction, the extended InfoMax Independent Component Analysis (ICA) method was applied. Independent Components (ICs) were automatically labeled and excluded using the MNE-ICLabel library [29], by retaining only ICs labeled as 'brain'. Finally, channel-level data were reconstructed from the ICs space.

2.5. Epochs, ERPs and regions of interest

Following the removal of artifacts, for each channel the continuous EEG signal was segmented into epochs. Each epoch was time-locked to the onset of the odor presentation. Because natural breathing was not time-locked to the stimulus onset, we specified two a priori 6-s windows (0–6 s stimulation and 6–12 s wash-out), followed by a 0–12 s aggregate window, to improve the signal-to-noise ratio and comparability across conditions.

To retain temporal sensitivity without inflating multiplicity or amplifying respiratory-phase jitter, we performed the analysis on smaller 1-s bins over the 0–12 s range, providing an indication of how EEG metrics vary (i.e., due to build-up or recovery) after the stimulation. Baseline correction was performed by subtracting from each epoch (0–12 s) the signal's mean amplitude within a pre-stimulus interval (from –1 to 0 s). Trials with residual artifacts (amplitude exceeding ± 100 μ V) were excluded from further analysis. For each channel and for each of the three olfactory stimulation trains (i.e., each sequence of 10 stimulations with a given odor), the related EEG epochs were averaged, so as to obtain an ERP signal.

Specific Regions of Interest (ROIs) were defined on the scalp, as clusters of EEG channels, using information derived from prior groupings [30–33] and the channel position on the scalp. In particular, the considered ROIs corresponded to frontal, central, temporal, parietal and occipital cortical regions, defined as follows (Fig. 1D):

- i. Frontal ROI (17 electrodes): AF7, AF3, Fp1, Fp2, AF4, AF8, F7, F5, F3, F1, F2, F4, F6, F8, AFz, Fpz, Fz;
- ii. Central ROI (14 electrodes): FC5, FC3, FC1, FC2, FC4, FC6, Cz, FCz, C5, C3, C1, C2, C4, C6;
- iii. Temporal ROI (6 electrodes): FT7, FT8, T7, T8, TP7, TP8;
- iv. Parietal ROI (16 electrodes): P7, P5, P3, P1, Pz, P2, P4, P6, P8, CP1, CP2, CP3, CP4, CP5, CP6, CPz;
- v. Occipital ROI (8 electrodes): PO7, PO3, O1, O2, PO4, PO8, Oz, Poz.

Within each ROI, ERPs detected by all its channels in response to each odor were averaged.

2.6. Early ERP processing in the time domain

Early effects on ERPs were studied in the time domain, by extracting for each odor the maximum difference in amplitude between any two channels at any temporal instant, as well as its related latency. This was performed within two temporal windows: 0–100 ms and 0–300 ms.

Furthermore, the maximum positive peak and the minimum negative peak, as well as their related latencies, were extracted from the ROI-averaged ERPs. This analysis was repeated both in the 0–100 ms and in the 0–300 ms windows.

2.7. Late ERP processing in the time domain

Late effects on ERPs were evaluated in the time domain, by quantifying the Global Field Power (GFP), defined as the time-dependent spatial standard deviation of the EEG signals across all considered channels:

$$GFP(t) = \sqrt{\frac{\sum_K (V_i(t) - V_{mean}(t))^2}{K}} \quad (1)$$

where $V_i(t)$ was the time (t)-dependent voltage of the i -th channel, $V_{mean}(t)$ was the time-dependent average voltage across all channels, and K was the number of channels. The GFP was averaged across trials for each subject and its temporal mean value was evaluated within distinct temporal windows: 0–12 s, 0–6 s and 6–12 s.

Furthermore, to investigate whether different effects of the different odors could be discriminated according to the whole GFP time-series, a GFP analysis was performed using both sliding-time windows (0–1 s, 0–2 s, 0–3 s, 0–4 s, 0–5 s, 0–6 s, 0–7 s, 0–8 s, 0–9 s, 0–10 s, 0–11 s) and fixed-time windows (0–1 s, 1–2 s, 2–3 s, 3–4 s, 4–5 s, 5–6 s, 6–7 s, 7–8 s, 8–9 s, 9–10 s and 10–11 s).

To statistically compare the GFP time-series across conditions, a permutation test ($N_{perm} = 5000$) was performed. For each of the 5000 permutations, subject-level data were randomly reassigned between the two conditions, preserving the original group sizes (15 subjects per condition). The GFP was averaged across subjects for each condition and the difference in average GFP between any two conditions was calculated at each time point. The resulting temporal mean served as the test statistical variable, which in the following is referred to as GFP observed difference. The distribution of this variable was used to estimate the p -value and 95% confidence intervals, allowing for a robust assessment of condition-related effects over time [34].

2.8. Late ERP processing in the time-frequency domain

Late effects of the different odors on ERPs were also analyzed in a time-frequency combined domain. This was achieved by processing the EEG epochs with Morlet wavelet transformations, focusing on frequencies in the range 3–30 Hz. The wavelets were configured to have a variable number of cycles, defined as half the frequency ($n_{cycles} = f/2$). The average across epochs was used to obtain the mean Time-Frequency Representation (TFR) of each subject.

For statistical purposes, TFRs were averaged among all channels and ROIs. From the averaged TFRs, the ERP absolute power was computed in specific frequency bands: 1–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alpha), and 13–30 Hz (beta). This analysis was conducted within the same temporal windows used for the previous analyses, i.e., 0–12 s, 0–6 s, and 6–12 s.

2.9. Statistical analysis

Peaks, latencies and absolute power were analyzed using paired non-parametric tests, focusing on group-level differences across conditions. In particular, two-way Friedman tests were adopted. When significant main effects were observed, pairwise differences were analyzed using Wilcoxon-Nemenyi-McDonald-Thompson post-hoc tests. To cope with the Family Wise Error Rate (FWER) problem, the Bonferroni correction was adopted whenever needed. Effect size was computed both at a group level and at a pair-wise level, via the Kendall's W and matched-pairs rank-biserial correlation (r_{bis}) test statistics, respectively, with a 95% Confidence Interval, calculated with 1000 bootstraps. The statistical significance level was always set at 0.05.

All statistical analyses were performed with the software IBM SPSS version 27 (SPSS Inc., Armonk, NY) and a Python-based custom code.

2.10. Habituation analysis

We assessed habituation by testing whether the signal's power changed monotonically with the number of trials (e.g., olfactory stimulations). Absolute power was analyzed in the two post-stimulus windows (0–6 s and 6–12 s), for each of the three conditions (pleasant, neutral and unpleasant stimuli). To ensure comparability among subjects, only the first nine trials were used for each subject. Within each trial, power was averaged across channels. A per-band analysis was performed, by computing the power within canonical bands (Delta 1–4 Hz, Theta 4–8 Hz, Alpha 8–13 Hz, and Beta 13–30 Hz).

For each set (subject $\times$ condition $\times$ window $\times$ frequency band), the relationship between the PSD and the number of trials was processed with a linear fit, after normalizing both variables with mean and standard deviation. Slopes were estimated with the Theil–Sen robust estimator, more robust than traditional linear fitting when handling outliers. The distribution of the subjects' slopes was tested against zero using a two-sided Wilcoxon signed-rank tests. Effect size for paired data (r_{bis}) and 95% bootstrap confidence interval were computed for the median slope, based on 1000 resamples.

3. Results

3.1. Time-domain analysis of early ERPs

Fig. 2 presents grand-average early ERPs (obtained by averaging ERPs across all subjects), gathered from all 64 channels in response to olfactory stimulations with the neutral, pleasant and unpleasant odors.

The maximum difference in ERP amplitude between any two channels at any temporal instant, as well as its latency, are presented in Fig. 3, for each olfactory stimulation and each considered temporal window (0–0.1 and 0–0.3 s).

Friedman tests revealed no statistically significant difference in latency among the conditions, both in the 0–0.1 s window ($F = 1.069$ (2), $p = 0.586$) and in the 0–0.3 s window ($F = 4.508$ (2), $p = 0.104$).

On the other hand, differences in maximum difference in amplitude were found to be significant at a group level in the 0–0.3 s window ($F = 10.133$ (2), $p = 0.006$, $W = 0.34$, 95% CI = [0.084–0.760]). In particular, post-hoc tests highlighted a significant difference for the neutral-pleasant comparison ($t = -3.020$, $p = 0.009$, $r_{bis} = -0.660$), which

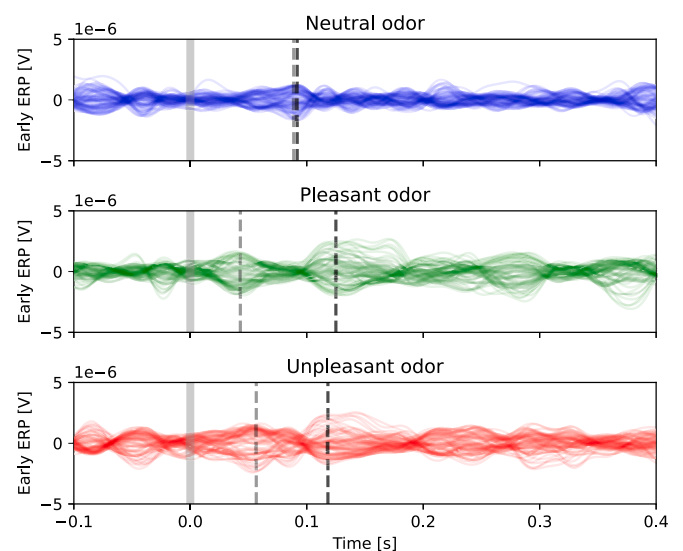


Fig. 2. Grand-average early ERPs elicited by the neutral, pleasant and unpleasant odors, for all 64 channels. The solid line indicates the stimulus onset instant ($t = 0$), while the dashed lines indicate the latency of the maximum difference in amplitude between any two channels, in the 0–100 ms window (grey line) and 0–300 ms window (black line).

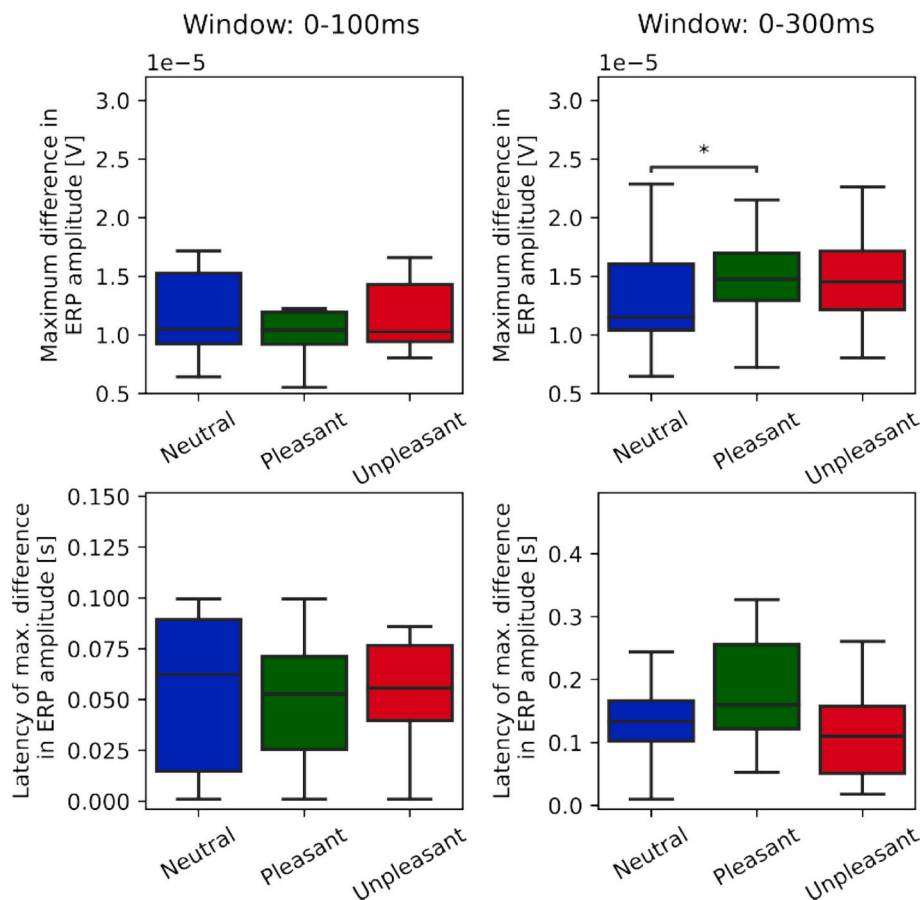


Fig. 3. Box plots comparing, among conditions, the maximum difference in early ERP amplitude between any two channels at any temporal instant (top panels) and the related latency (bottom panels). Data are reported for both the considered temporal windows (0–0.1 and 0–0.3 s). Statistically significant differences are indicated with an asterisk (see the text for statistical outcomes).

also survived FDR correction ($p_{\text{ADJ}} = 0.027$), as indicated in Fig. 3. Fig. 4 presents ROI-averaged early ERPs elicited by the different olfactory stimulations.

Statistical comparisons of positive and negative peaks in the 100 ms window did not yield any significant result for the frontal, central, temporal, and parietal ROI.

However, in the occipital lobe, each signal showed early negative peaks, which, for the unpleasant and pleasant odors, occurred earlier than that for the neutral odor (Fig. 4). In particular, the earliest negative peak's median latency was 0.071 s [IQR = 0.038], 0.041 s [IQR = 0.025] and 0.046 s [IQR = 0.050] for the neutral, pleasant and unpleasant stimulations, respectively ($F = 9.390$ (2), $p = 0.009$, $W = 0.308$, 95% CI = [0.124, 0.622]). Post-hoc tests showed that both neutral-pleasant and neutral-unpleasant comparisons survived the FDR correction (p_{ADJ} equal to 0.009 and 0.047, respectively), indicating that non-neutral stimulations caused significantly earlier negative peaks, relative to the neutral odor. Therefore, for both the pleasant and unpleasant odors, early ERPs in the occipital region showed negative deflections at ~ 40 ms (N40 peaks). Extending the search to the 300 ms window, as well as to positive peaks, did not yield any significant result, both for the occipital ROI and for each other ROI.

3.2. Time-domain analysis of late ERPs

Fig. 5 presents the grand-average GFP associated to late ERPs.

The GFP response analysis across the three stimulation conditions (neutral, pleasant and unpleasant odors) revealed significant differences within specific temporal windows. In particular, the GFP signal displayed a marked reduction in amplitude during the olfactory stimulation

period (0–6 s), for each condition, with a greater decrease observed for the pleasant and unpleasant odors, compared to the neutral one (Fig. 5).

To statistically assess differences in GFP mean value among the conditions, a Friedman test was conducted, for each temporal window. The results showed a significant main effect of condition within the 0–12 s window ($\chi^2 = 6.93$ (2), $p = 0.031$, $W = 0.231$, 95% CI = [0.058–0.564]) and the 0–6 s window ($\chi^2 = 6.93$ (2), $p = 0.031$, $W = 0.231$, 95% CI = [0.084–0.551]), whereas no significant differences were found in the 6–12 s window ($\chi^2 = 3.33$ (2), $p = 0.189$).

Post-hoc comparisons with Bonferroni correction revealed that, within the 0–12 s windows, the pleasant stimulus elicited a significant decrease in GFP mean value, compared to the neutral odor ($p = 0.040$), as presented in Fig. 6.

However, no significant differences were observed between the neutral and unpleasant odors ($p = 0.221$), and between the pleasant and unpleasant odors ($p = 1$).

Similarly, within the 0–6 s window, the pleasant odor elicited a significant drop in GFP mean value, relative to the neutral one ($p = 0.018$), while comparisons between the neutral and unpleasant odors ($p = 0.093$), and between the pleasant and unpleasant odors ($p = 1.000$), did not reach significance.

We then investigated whether the different olfactory stimulation conditions could be distinguished by comparing the GFP time series within smaller temporal windows, using both sliding-time and fixed-time windows. Fig. 7 presents the results.

By using a sliding-time window with increments of 1 s (Fig. 7A), the difference between two conditions was maximal in the 0–8 s window, both for the neutral-pleasant (GFP observed difference = 4.29×10^{-7} V, $p < 0.001$) and the neutral-unpleasant (GFP observed difference = 3.50×10^{-7}

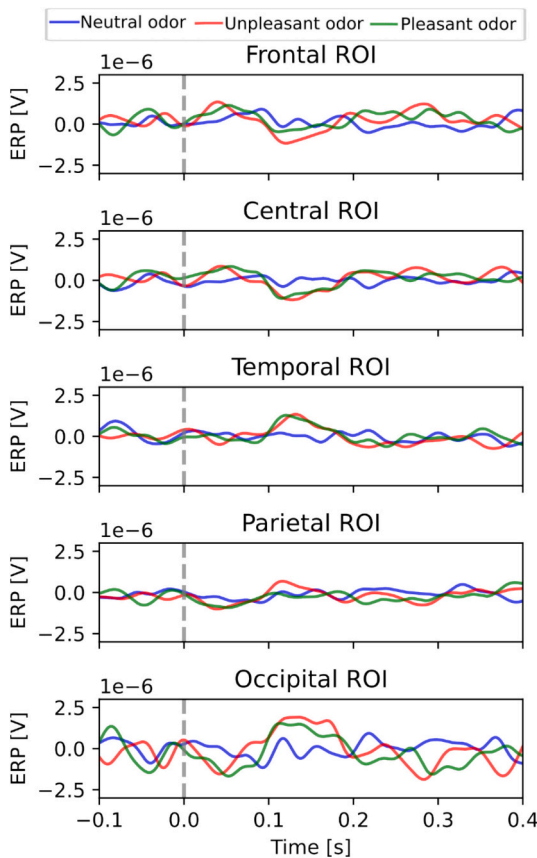


Fig. 4. Grand-average early ERPs detected within each ROI in response to the neutral, pleasant and unpleasant odors. The grey dashed line marks the olfactory stimulus' onset.

V, $p = 0.012$) comparisons.

When using a fixed-time window of 1 s (Fig. 7B), the difference between the conditions was maximal in the 3–4 s window, both for the neutral-pleasant (GFP observed difference = $6.22\text{E-}7$ V, $p < 0.001$) and the neutral-unpleasant (GFP observed difference = $5.42\text{E-}7$ V, $p = 0.009$) comparisons.

3.3. Time-frequency analysis of late ERPs

Results of the Morlet wavelet-based analysis of late ERPs in the time–frequency combined domain are presented in Fig. 8, both jointly for all channels and separately for each ROI. From the time–frequency representation, the mean power of late ERPs was computed within each band, for all channels and each ROI, as well as within each temporal window (0–6 s, 6–12 s and 0–12 s), as reported in Fig. 9.

The all-channel analysis showed no significant difference among conditions in the δ and θ bands, for each temporal window. In the α band, significant differences were achieved in the 0–12 s ($\chi^2 = 6.933(2)$, $p = 0.031$; $W = 0.231$, 95% CI = [0.053–0.618]) and 0–6 s ($\chi^2 = 10.133(2)$, $p = 0.006$; $W = 0.338$, 95% CI = [0.164–0.653]) windows. Post-hoc analysis revealed a decrease in power for the pleasant stimulation relative to the neutral one (0–12 s: $p = 0.027$, $r_{\text{bis}} = 0.661$; 0–6 s: $p = 0.0280$, $r_{\text{bis}} = 0.655$) and for the unpleasant stimulation relative to the neutral one (0–12 s: $p = 0.029$, $r_{\text{bis}} = 0.651$; 0–6 s: $p = 0.024$, $r = 0.678$), as indicated in Fig. 9. Similarly, in the β band, a significant desynchronization was observed in the 0–6 s window ($\chi^2 = 14.933(2)$, $p = 0.001$; $W = 0.498$, 95% CI = [0.280–0.764]); post-hoc analysis confirmed a reduction in power for the pleasant and unpleasant stimulations relative to the neutral one (pleasant vs neutral: $p = 0.009$, $r_{\text{bis}} = 0.807$;

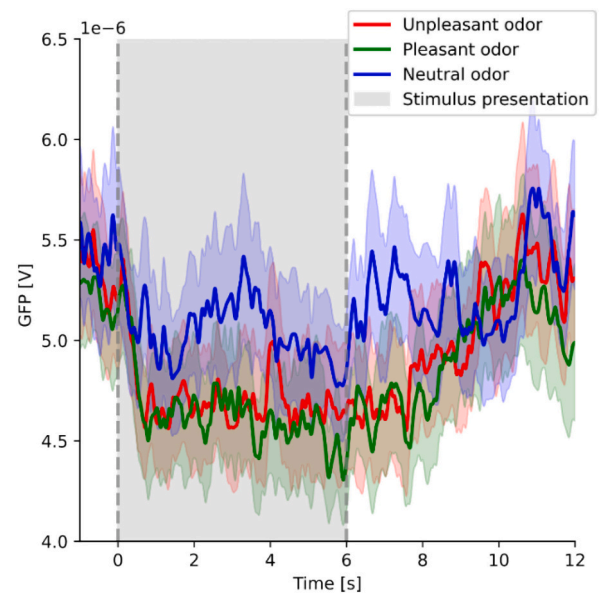


Fig. 5. Grand-average GFP of late ERPs in response to the neutral, pleasant and unpleasant odors. The grey dashed lines mark the olfactory stimulation's duration. The colored shade around each curve corresponds to the GFP standard deviation among the subjects.

unpleasant vs neutral: $p = 0.012$, $r_{\text{bis}} = 0.776$), whereas other windows were not significant.

The ROI-specific analysis showed that δ power was not significantly (Friedman test) affected by the olfactory stimulation, for any temporal window (Fig. 9). Alpha power was found to decrease after both pleasant and unpleasant stimulation (compared to the neutral one) within the 0–6 s window, in the central ($\chi^2 = 8.133(2)$, $p = 0.017$; $W = 0.271$, 95% CI = [0.071–0.618]; neutral vs pleasant: $p = 0.022$, $r_{\text{bis}} = 0.685$; neutral vs unpleasant: $p = 0.028$, $r_{\text{bis}} = 0.654$), parietal ($\chi^2 = 8.133(2)$, $p = 0.017$; $W = 0.271$, 95% CI = [0.084–0.618]; neutral vs pleasant: $p = 0.037$, $r_{\text{bis}} = 0.617$; neutral vs unpleasant: $p = 0.043$, $r_{\text{bis}} = 0.596$), and occipital ($\chi^2 = 10.133(2)$, $p = 0.006$; $W = 0.338$, 95% CI = [0.093–0.724]; neutral vs pleasant: $p = 0.0343$, $r_{\text{bis}} = 0.627$; neutral vs unpleasant: $p = 0.022$, $r_{\text{bis}} = 0.688$) regions. Similarly, but with a more marked significance, β power was found to decrease after both pleasant and unpleasant stimulation (compared to the neutral one) within the 0–6 s window, in the frontal ($\chi^2 = 12.400(2)$, $p = 0.002$; $W = 0.413$, 95% CI = [0.231–0.671]; neutral vs pleasant: $p = 0.002$, $r_{\text{bis}} = 1.014$; neutral vs unpleasant: $p = 0.0031$, $r_{\text{bis}} = 0.952$), central ($\chi^2 = 14.400(2)$, $p = 0.001$; $W = 0.480$, 95% CI = [0.271–0.760]; neutral vs pleasant: $p = 0.001$, $r_{\text{bis}} = 1.074$; neutral vs unpleasant: $p = 0.005$, $r_{\text{bis}} = 0.891$), and parietal ($\chi^2 = 14.933(2)$, $p = 0.001$; $W = 0.498$, 95% CI = [0.280–0.764]; neutral vs pleasant: $p = 0.006$, $r_{\text{bis}} = 0.868$; neutral vs unpleasant: $p = 0.001$, $r_{\text{bis}} = 1.122$) regions.

3.4. Habituation analysis

In the per-band analysis, none of the combinations between band (delta, theta, alpha, beta), window (0–6 s, 6–12 s), and condition (pleasant, neutral, unpleasant) yielded a slope distribution different from zero after FWER correction (Fig. 10). Median slopes hovered near zero, effect sizes were small, and the bootstrap confidence intervals for the medians included zero. Therefore, the results indicate no systematic habituation of band-limited EEG power across trials, arguing against cumulative adaptation, fatigue, or order effects and supporting the interpretation that alpha/beta desynchronizations reflect sustained odor processing rather than progressive drift.

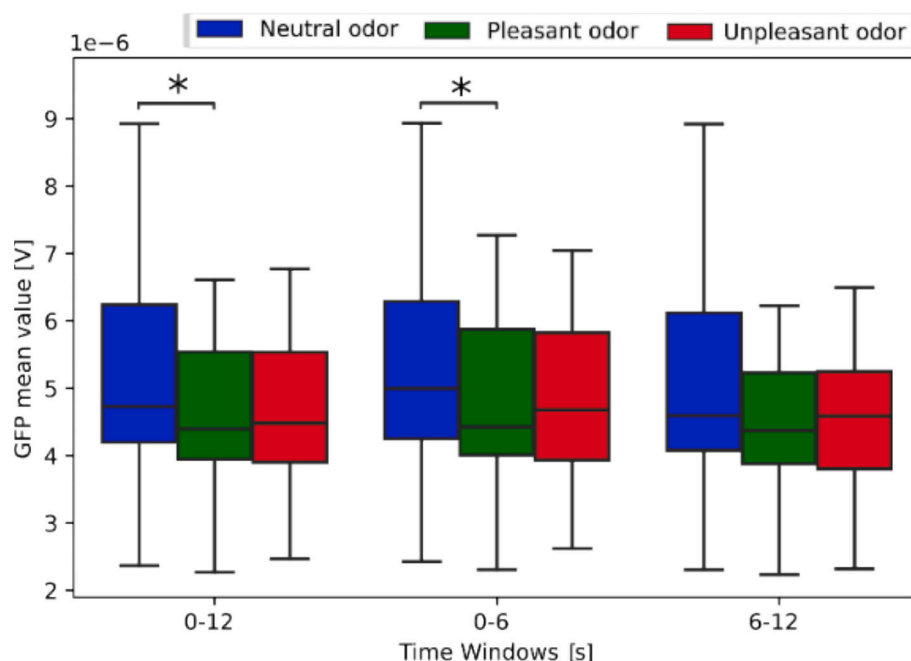


Fig. 6. Box plots of the GFP mean value, quantified for all subjects within different temporal windows, in response to the neutral, pleasant and unpleasant odors. Statistically significant differences are indicated with asterisks (see the text for statistical outcomes).

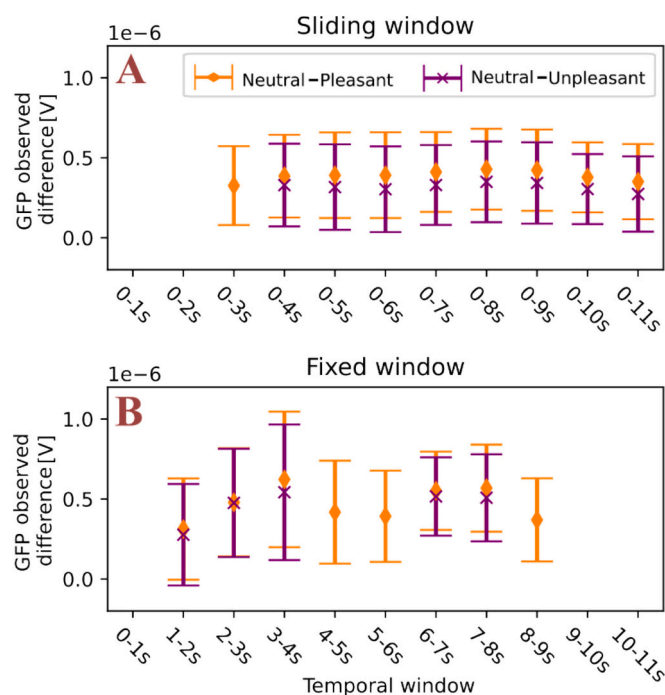


Fig. 7. Results of the permutation tests between GFP time series of any two conditions, with sliding-time (A) and fixed-time (B) windows. Only significant comparisons ($p < 0.05$) are reported. The pleasant-unpleasant comparison never produced significant results.

4. Discussion

4.1. Hedonic valence-independent early ERP responses

Early ERP analyses revealed larger responses to both pleasant and unpleasant odors, in comparison to those to the neutral one. Such an increase in evoked EEG amplitude is consistent with previous studies on

brain activations, using either EEG [2,14] or functional magnetic resonance imaging [35,36].

In particular, early ERPs presented, in the occipital cortex, distinct negative deflections at ~ 40 ms (N40 peaks), regardless of the odor's hedonic valence. While an early occipital component in response to an olfactory stimulation may seem unexpected, several features of our protocol reduced the likelihood that it was due to a non-olfactory input: recordings were eyes-closed throughout, the room was dim and free of visual cues, and mechanical sounds associated with opening/closing of the nebulizer caps were constant across odors, minimizing any odor-contingent auditory transients. On the other hand, the result is consistent with previous findings that reported significant early ERP modulation in response to non-neutral stimuli [8,37]. Such early peaks in the occipital cortex may be interpreted as manifestations of initial cortical processing of olfactory information, as occipital responses are typically linked to early sensory processing across various sensing modalities [38,39].

Mechanistically, occipital engagement can arise via cross-modal/top-down influences during olfactory processing. In particular, human neuroimaging and neuromodulation studies indicate that the visual cortex can be recruited, with possible causal contributions, to odor perception via imagery/prediction mechanisms [36,40–42]. For example, repetitive transcranial magnetic stimulation over the early visual cortex was shown to improve fine odor discrimination, consistently with odor-evoked imagery rather than exogenous visual input [41]. Moreover, fMRI studies demonstrated olfactory–visual interactions (e.g., picture–odor congruency paradigms), supporting functional coupling between visual areas and chemosensory processing [36,43]. Furthermore, evidence of early occipital ERP modulations in multisensory contexts revealed that the visual cortex is rapidly influenced by nonvisual inputs [42,44].

It is also worth noting that N40 peaks have previously been reported in visually unrelated potentials (e.g., auditory and somatosensory), reflecting activations of fast sensory pathways; they may correspond to the sensory imagery/registration phase, as an essential part of early sensory processing [45–47].

Consistent evidence also comes from a landmark H_2^{15}O -PET study in healthy adults, which compared olfactory naming (ON, i.e., naming a

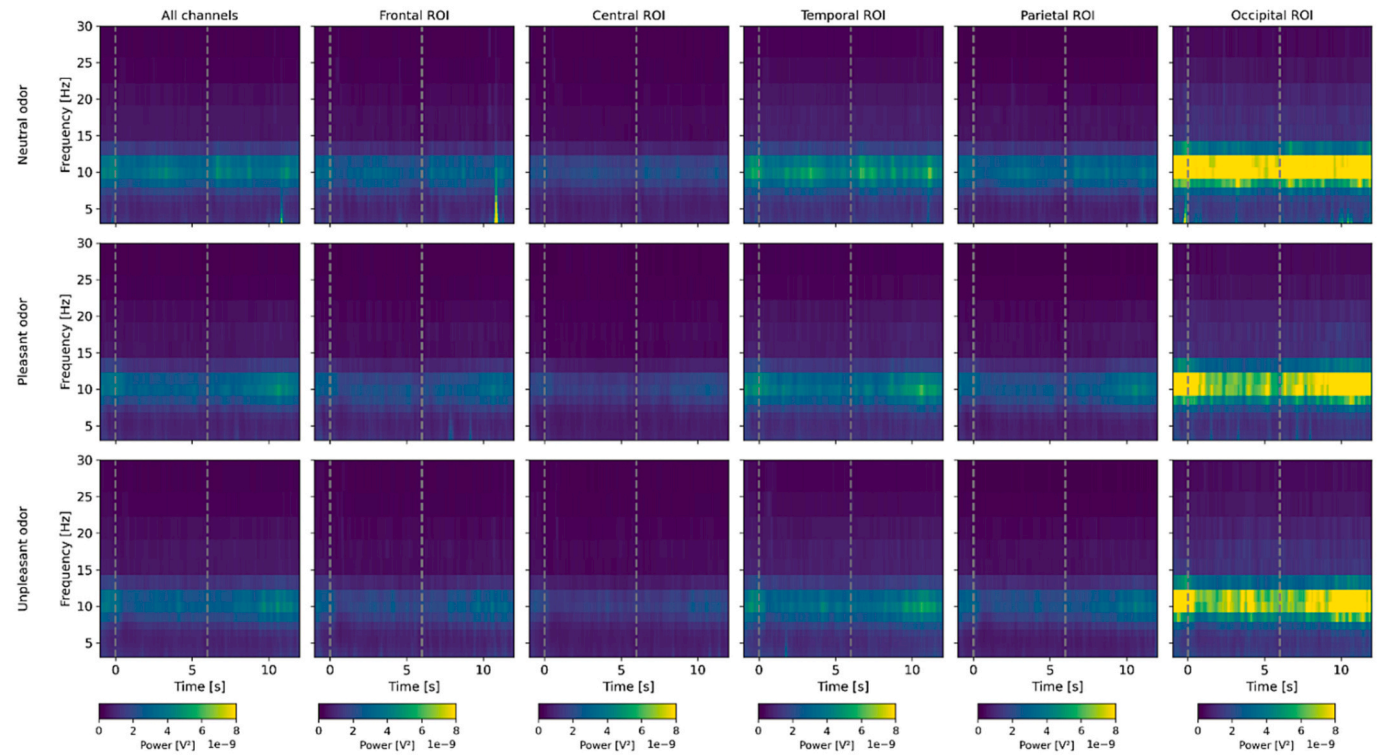


Fig. 8. Morlet wavelet-based time-frequency spectrograms of late ERPs, averaged across trials and among all subjects. The spectrograms are mapped according to all possible combinations among the different ROIs and olfactory stimulation conditions. Each panel shows a map of the signal power (color-coded), as a function of time and frequency. The grey dashed lines mark the duration of the olfactory stimulation.

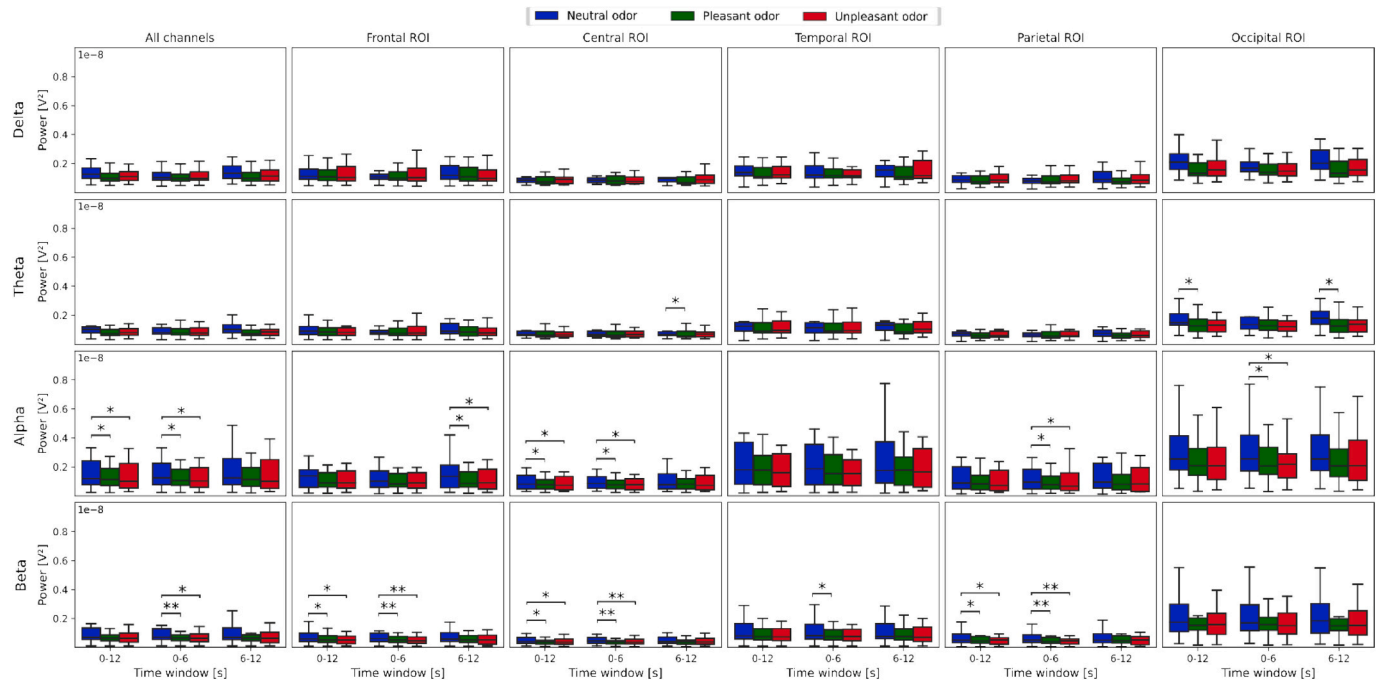


Fig. 9. Mean power (averaged within ROIs and windows) of late ERPs elicited by the neutral, pleasant and unpleasant odors. Statistically significant differences are indicated with asterisks (see the text for statistical outcomes).

familiar odor) and olfactory matching (OM, i.e., differentiating unfamiliar odors) [40]. That investigation on brain activity beyond low-level smelling revealed how, during the ON task, brain activation included the left cuneus, right anterior cingulate, left insula and bilateral cerebellum. During the OM task, activation included the left cuneus and cerebellum.

The region found to be specific for olfactory naming in the cross-task contrast was the left cuneus (a visual cortical region) — interpreted as suggesting engagement of visual imagery/semantic processes during odor naming, again pointing to higher-order, object-level odor processing rather than primary olfactory cortex activity alone.

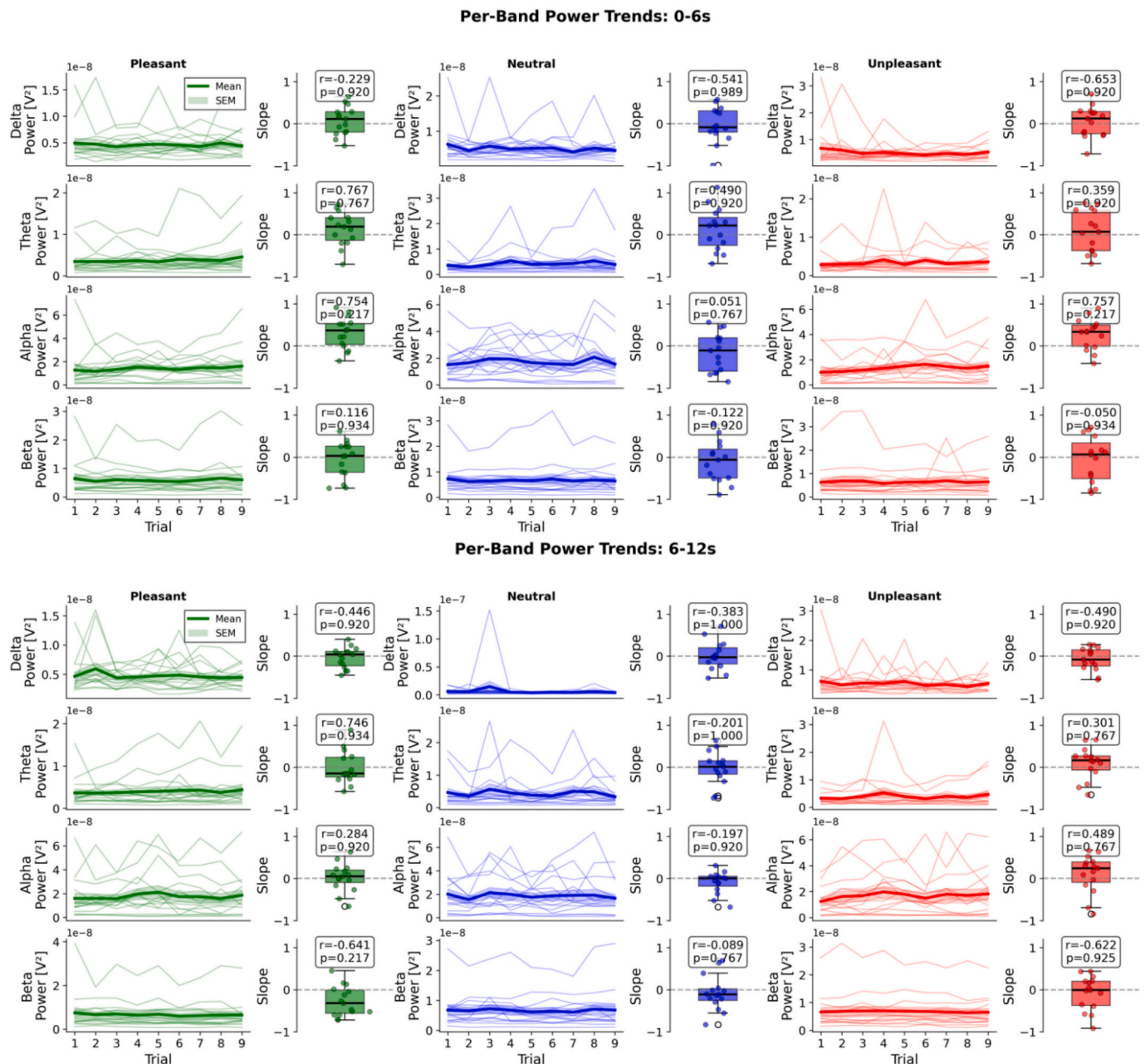


Fig. 10. Per-band (delta, theta, alpha, and beta) mean power of late ERP (averaged within channels) represented across trials, for each time window, and each stimulation condition. In each graph, the thin interpolating lines represent individual participants, while the thick line corresponds to the group mean, and the shaded area is the mean standard error (SEM: Standard Error of the Mean). The boxplots display the patient-wise distribution of the linear interpolation's slope. Effect size r_{bis} and significance p are reported from the two-way Wilcoxon test after FWER correction.

According to those findings, the early occipital negativity (N40) observed in this study may reflect the earliest phase of a global suppression/engagement pattern (i.e., the transition into a sustained processing state), rather than visual processing per se. This is also consistent with observations of similar early occipital peaks associated with emotional and sensory processing during odor habituation paradigms in humans [48,49] and dogs [50].

Taken together, these considerations provide a principled account for a possible interpretation of the occipital N40 component observed in our eyes-closed, non-visual, olfactory stimulation protocol: an early, valence-independent node within a distributed olfactory network that leverages cross-modal imagery/prediction to support subsequent sustained processing.

4.2. Hedonic valence-independent late ERP responses

The GFP vs time analysis provided useful insights on temporal changes in the spatial variability and global dynamics of late ERP responses. During the stimulation window, the GFP decreased in the stimulation window (0–6 s) relative to the post-stimulus interval (6–12 s), indicating a lower-amplitude and a more spatially homogeneous scalp field distribution. This is a canonical signature of a system that settles into stable processing, rather than transient orienting [51,52].

The time–frequency analyses in the 0–6 s window conjointly showed widespread alpha (8–12 Hz) and beta (13–30 Hz) decrease for both odors versus the neutral control, which were maximal over frontal/central/parietal regions for beta waves with broader posterior extension

for alpha waves. These patterns reversed after the stimulation (6–12 s), underscoring linkage to ongoing olfactory processing rather than nonspecific factors. According to an established interpretative framework, decrease in alpha power reflects gating-by-inhibition (release of functional inhibition and increase of information throughput [53]), whereas decrease of beta power encodes a shift away from a “status-quo” sensorimotor/attentional set, toward active input processing [54], mechanistically consistent with sustained sampling during continuous chemosensory stimulation.

Recent time-frequency studies provided more direct benchmarks for this pattern. Gallus et al. reported odor-related alpha desynchronization beginning approximately 1.3 s after onset and persisting throughout a 5-s trial, with central and occipital maxima [55]. Such timing and topography are consistent with the sustained alpha decrease and the maximal neutral/non-neutral separation at 3–4 s found in our study, even though in [55] there were simultaneous visual stimuli, while in our case the eyes were closed. Yao et al. showed that two odors matching for perceived intensity and pleasantness produced different resting-state alpha and beta-gamma activity and network organization, identifying arousal as an olfactory dimension separable from valence [56]. Accordingly, the absence of pleasant-unpleasant contrast in our study might be interpreted as a shared scalp-level engagement response under passive sustained exposure, rather than evidence that the two odors were neuro-physiologically equivalent. At the circuit level, Nordén et al. found that subjective odor valence is communicated from the olfactory bulb to the piriform cortex in the early gamma band, followed by a feedback signal from the piriform cortex to the olfactory bulb in the later beta band [57]. While this differs from our valence-independent scalp alpha/beta power, it is worth noting that the measures are complementary: directed bulb-piriform connectivity with trial-wise perceptual ratings might isolate valence-specific codes, which may be obscured by ROI-averaged scalp power, particularly in a no-task, non-sniff-locked paradigm.

In contrast, we observed no robust frontal-theta wave effects. This aligns with prior evidence that piriform-hippocampal frontal-midline theta activity is strongest when time-locked to an inhalation onset [8]. In our study design, the non-sniff-locked, natural-breathing-based protocol intentionally limited the risk of inspiration-related transients and motor/respiratory confounds [8,58]. This rationale also motivated a 0–6 s stimulation window paired with a 6–12 s wash-out window of equal duration, whose length ensured: i) statistical comparability between segments of equal length; ii) independence from respiratory-phase jitter, taking advantage of a sufficiently long epoch (and stimulus).

Ghibaudo et al. observed that, during a ten-minute exposure to a personally selected pleasant odor, slower breathing and enhanced respiration-locked EEG modulation over a bilateral temporo-parieto-central network [59]. This spatial convergence with our central/parietal effects supports distributed sustained processing, while indicating that simultaneous nasal-flow recording will be needed to separate odor-driven desynchronization from valence-related brain-respiration coupling.

Additionally, consecutive odor delivery and the fixed 1-s window analysis allowed us to show that the contrast between neutral and non-neutral odors grew with time and peaked in the 3–4 s bin, with no pleasant–unpleasant difference (Fig. 7B). Moreover, the sliding-window analysis revealed that the cumulative difference was largest over 0–8 s (Fig. 7A). These outcomes are indicative of ramp-and-hold dynamics: an initial orienting response was followed by a progressive reduction and spatial homogenization of the GFP and concomitant alpha/beta power decrease, which settled into a quasi-steady state by ~3 s. Such a mid-stimulation build-up is more compatible with stabilization under continuous odor delivery (i.e., the establishment of a sustained, engaged processing state) rather than with brief, onset-locked attentional spikes. Indeed, the latter would be expected to yield early (0–1 s) confined effects, with a rapid decay. Nevertheless, despite such an interpretation,

we acknowledge the direct respiration monitoring as a possible limitation, which might be addressed by future work.

Supporting evidence toward the fact that the observed effects were related to the stimulation condition (rather than trial drift) derives from the habituation analysis. The latter revealed no significant trends for any band in any condition, arguing against attention-driven drifts across trials. Moving-window analyses showed persistent alpha/beta behaviours with consistent topography. Moreover, pre-stimulus baselines did not drift with trial/block order. Overall, these analyses suggest that between-subject variability in natural breathing depth/rhythm did not appear to undermine the main effects.

4.3. Possible confounding factors: Odorant administration and sex balance

While power and GFP variations appeared valence-independent within the experimental stimulus set and sample size, such independence should be taken cautiously, avoiding generalizations to different odorants. Indeed, while hedonic ratings usually show regularities across different families of chemical compounds [20,22] and cultures [21], a broader generalization would require larger samples and multiple exemplars per valence. We also note that odor intensities were not psychophysically matched across conditions. Indeed, while each odorant was delivered at its undiluted concentration and was held constant across participants, perceptual equality across participants was not ensured. This is due to the fact that intensity growth functions differ across odorants (according to the Stevens' power law with compound-specific exponents) and inter-individual sensitivity varies [60].

Furthermore, beta/gamma dynamics in the olfactory bulb and piriform cortex have been shown to track trial-wise perceived odor intensity, whereas evidence for a corresponding relationship with physical odor concentration was weak [61]. This reinforces the limitation of our study: fixed, undiluted concentrations do not guarantee matched neural input, such that future studies should combine within-participant intensity matching with trial-level ratings.

Moreover, as the stimulation conditions differed not only in odor but also in liquid vehicle, it cannot be excluded that the EEG responses also had a perceptual component determined by the liquid vehicle, possibly through trigeminal receptor activations, beyond olfaction. For instance, trigeminal pathways are known to be recruited by sulfur-containing volatiles [62]. This implies the need for taking into account in future investigations possible olfactory-trigeminal interactions. This might be addressed using vehicle-matched controls (vehicle-only conditions) and/or odorants with a common solvent.

We also note that, despite the fact that the subjects self-reported normosmia, had a young age, and had no previous comorbidity, the data might also reflect inter-subject variability in olfactory capabilities of unknown significance. Furthermore, it is worth stressing that the cohort was not sex-balanced (67% women). As sex-related differences may occur in olfactory sensitivity, hedonic judgments, and chemosensory processing, the sex distribution of this study's sample may limit generalizability of its outcomes. Despite the within-subject design mitigated between-subject variability by comparing each participant to themselves across conditions, sex-by-condition interactions cannot be excluded. Future studies should therefore treat sex as a moderator to test possible sex-by-condition interactions.

5. Conclusions

This study investigated cortical responses to olfactory stimuli differing in hedonic valence (pleasant, unpleasant and neutral), focusing on both early and late EEG evoked potentials. Continuous olfactory stimulation for 6 s promoted sustained neural engagement, providing insights on olfactory processing dynamics.

Unlike prior studies that relied on brief or intermittent stimuli, sustained stimulations enabled the observation of prolonged and

widespread cortical desynchronizations, particularly in frontal, central and parietal regions, and especially in alpha and beta bands. These findings highlight the existence of persistent and distributed high-frequency cortical processing during odor intake.

These outcomes were found to be independent of the odors' hedonic valence. To further enhance understanding of olfactory processing, several future developments may encompass various aspects, such as multimodal recordings, combining EEG with functional near-infrared spectroscopy, the use of personalised odorants with subject-specific hedonic valence, and the application of odd-ball paradigms to estimate the effect of deviant olfactory stimuli [63,64].

Moreover, given the implications on sustained neural impact of odors, future research may investigate the therapeutic (and neurophysiological) potential of prolonged exposure to specific odors [65–69].

CRediT authorship contribution statement

Piergiuseppe Liuzzi: Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Anna Maria Monciatti:** Investigation. **Rachele Burali:** Investigation. **Gabriele Frediani:** Methodology, Investigation. **Andrea Mannini:** Formal analysis. **Antonello Grippo:** Formal analysis. **Federico Carpi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Code and data to reproduce results in the manuscript are available at the following GitHub (<https://github.com/PeppeDrone/OERP-Healthy>). Raw data are available from the corresponding author upon reasonable request.

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