

Review

Chemosensory Perception: A Review on Electrophysiological Methods in “Cognitive Neuro-Olfactometry”

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Abstract: Various brain imaging techniques are available, but few are specifically designed to visualize chemical sensory and, in particular, olfactory processing. This review describes the results of quantitative and qualitative studies that have used electroencephalography (EEG) and magnetoencephalography (MEG) to evaluate responses to olfactory stimulation (OS). EEG and MEG are able to detect the components of chemosensory event-related potentials (CSERPs) and the cortical rhythms associated with different types of OS. Olfactory studies are filling the gaps in both the developmental field of the life cycle (from newborns to geriatric age) and the clinical and basic research fields, in a way that can be considered the modern “cognitive neuro-olfactometry”.

Keywords: EEG; OERP; CSERP; Olfactory Stimulation; Olfactory Perception; Chemical detection Systems

1. Introduction to Electrophysiological Techniques and Chemical Perception

Neuroimaging techniques allow us to investigate the neuronal mechanisms underlying information processing, and are an indispensable tool in efforts to gain a greater understanding of how human behaviour is related to sensations and perceptions. Several brain imaging techniques are available, but few are specifically designed for investigating chemical sensory and, in particular, olfactory processing. In this work, we evaluate two techniques based on electrophysiology: electroencephalography (EEG) and magneto-encephalography (MEG) (described in Section 2).

EEG is an electrophysiological and psychophysiological tool that can detect objective effects in olfactory and chemical research contexts, as well as in the medical olfactory field [1]. It is also widely used in olfactory research paradigms, to record responses to chemosensory stimulation. The first study to record responses of this type was carried out by Kobal [2], and since then EEG has become the main investigative tool for evaluating olfactory abilities and olfactory responses to chemosensory stimuli objectively [3].

The detection of pure olfactory perception is extremely complex, because olfactory perception has a strong cross-modal component [4–6]. Many brain structures (e.g., the anterior olfactory nucleus, anterior cortical amygdaloid nucleus, periamygdaloid cortex, entorhinal cortex, perirhinal cortex, piriform cortex, and olfactory tubercle) are activated or inhibited during olfactory processing, and study with neuroimaging tools has allowed the identification of an olfactory map, based on inhibitory and excitatory interactions [7–9]. Hand in hand with the important discoveries in the olfactory field mentioned above, there has been a progressive increase in the use of EEG in association with chemosensory stimuli, including the development of techniques for investigating chemosensory event-related potentials (CSERPs) and olfactory event-related potentials (OERPs).

The methodology used to elicit OERPs or CSERPs is the same as for electrophysiological perceptual potentials for physical stimuli. It is important to underline that at the sensory and perceptive level, there is a difference between “physical” stimulation and “chemical” stimulation. According to the classification of sensory receptors [10,11], receptors respond to different characteristics of the stimulus, depending on the receptor class to which they belong. The main receptors for physical stimuli are photoreceptors and mechanoreceptors, while the receptors for chemical stimuli are called chemoreceptors. The OERP is a cortical response that starts from the chemoceptive response, which derives from chemical stimulation by the odorous substance and, even if minimal, also has a mechanoreceptive component, due to the air pressure that reaches the nostril [12]. When the stimulus is administered to the subject, it must be sent in a very precise manner and with a very tight methodological control (e.g., environmental temperature control, environmental humidity control, control of the stimulation substance) [13–15]. In fact, while a given, purely physical stimulus (e.g., a spot of light) does not vary qualitatively or quantitatively, depending on the external temperature or humidity, and its transmission speed in the air it has a very low variability if we observe it with psychophysical methods; it happens otherwise for chemical stimuli, which are more susceptible to variations, also depending on environmental parameters [16–18]. To get an OERP, the onset of the stimulus must be triggered in the EEG, an element that allows the subsequent analysis with average for the extrapolation of the event-related potentials (ERP) components. What varies is a longer duration, both of the stimulus presentation and the inter-stimulus interval (ISI); being a chemical stimulus and not a physical one, the ISI must have a longer duration to avoid sensory habituation [15]. Sensory habituation is a physiological phenomenon that is particularly evident in the sense of smell [14,19–21]. The olfactory stimulus, if perceived for a frequent and continuous time decreases its sensory power; this phenomenon is also visible with OERPs, where repeated olfactory stimulations decrease the amplitude of the OERP components [22].

The minimum number of electrodes used for OERP registration is three (i.e., Fz, Cz, Pz), referenced mono-polarly and grounded to the forehead [17,23] or referred to linked mastoids and grounded to Oz [22]. The passband filter usually used is 0.01–30 Hz, 6 Db/Octave [17]. To obtain a defined OERP, identifiable in its components, a minimum of 10–30 averaged and artefact-free trials can be processed [23]. The temporal window depends on the task and the stimulus, and can vary in the range of –1 to +3 s [22], according to the components involved in the task. The problem of artefacts, elicited during an EEG olfactory recording, depends fundamentally on the type of the experimental task that is required. The EEG artefacts can normally be caused by small muscular contractions of the face, due to the inhalation of the chemical substance through breathing. This can be solved by using a good olfactometer, which allows a correct and precise stimulation so that the subject is free to breathe and inhale without having to make many muscular adjustments (especially those of the face, which are very easily recorded by the electrodes). This is especially true when trigeminal stimuli are used, which can induce a sensation sometimes associated with discomfort, or in some cases, pain [24–26]. Baseline correction normally occurs, as with other ERP techniques. Usually a baseline of –100 ms is sufficient for a proper alignment of the epochs in which the ERPs components are located. There are no substantial differences between the OERP averages that follow the normal ERP processing, as the tasks with OERP can take into account many electrophysiological aspects; these aspects do not depend on whether the stimulus is chemical or not, but on the type of component the researcher needs to consider.

Figure 1 shows a subject during a simple olfactive task in EEG. The subject freely inhales inside a black box that is interfaced with an olfactometer, which delivers chemical stimulations. In this condition, the black box allows the subject to have no other visual stimulation and to breathe while the stimulus is delivered. This is only one of the possible olfactory stimulation conditions, which can occur, for example, in a single nostril, in both nostrils [27,28], with visual sensory stimulation, and with cross-modal stimulation [29].

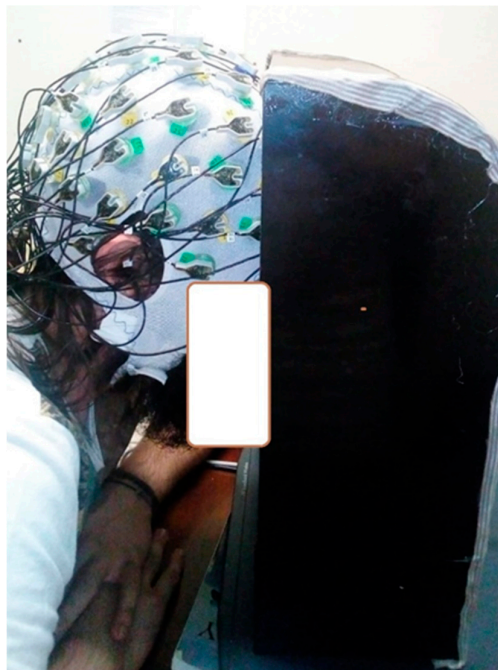


Figure 1. Example of an olfactory task in electroencephalography (EEG). The subject is freely inhaling inside a black box, from which different odourants are administered through an olfactometer.

Like ERP studies, which have shown greater age-related modulation [30–34], CSERP studies have also highlighted that chemosensory perception can have a variability that is age-related [17,31,35,36]. In a study by Kobal and Hummel, it was shown that aging is accompanied by a decrease in OERP sensitivity, as well as by a greater tendency to olfactory adaptation and a sensitivity threshold that is slower to recover [37].

Furthermore, another source of variability is strongly related to the responses of concentrations of different odourants [38] (see Figure 2).

Another field of olfactory EEG research is linked to the qualitative difference of the odours: for example, pure odourant (e.g., Phenethyl alcohol) [39], chemical stimuli that elicit trigeminal responses (e.g., menthol and CO₂) [40–44], social odour (e.g., body odour) [45,46], putative pheromones (e.g., 5 α -Androst-16-en-3 α -ol and Estradiol) [47–49], or odourless volatilized chemical compounds (e.g., Vaseline oil, air, and water) [23,50]. Odorless chemical compounds are used as control stimulations, sham stimulations, or substances that allow the dilution of odourants.

Each of all these stimulations (qualitatively different from the chemical viewpoint) produces a different response, both with respect to sensory aspects and perceptual aspects (see Figure 2). For example, Phenethyl alcohol (PEA) is considered a non-trigeminal odourant [39,51,52], and can elicit pure olfactory stimulation (see Figure 2).

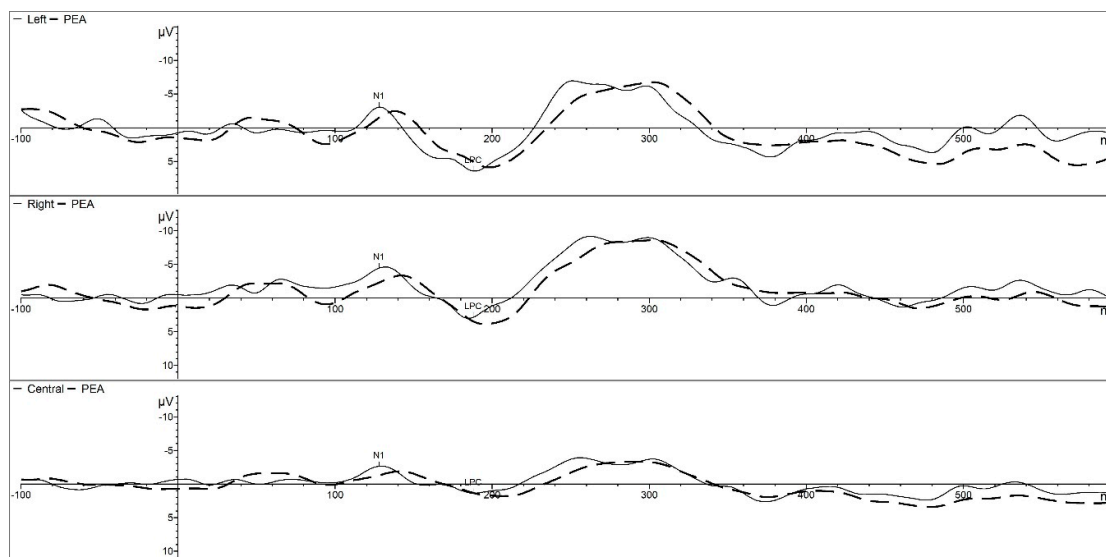


Figure 2. Example of olfactory event-related potentials (OERPs): comparison of two different concentrations of Phenethyl alcohol (PEA) in the right, left, and central regions of interest (ROI). PEA smell is considered to be an odourant that does not elicit a trigeminal stimulation. The solid line refers to the highest concentration of PEA. The dashed line refers to the lower PEA concentration. N1 is the first negative component, LPC is the late positive component.

Pause's research group used chemosensory stimulation (i.e., social odour) to probe perceptive response in subjects that smelled samples containing their own body odour or the body odours of others. The results of this study showed that subjects are able to differentiate between body odours [53].

The distinction between the social odour and the putative pheromone is intended as a different methodological management of the odourants. Body odour (e.g., underarm odour) is usually used to evaluate effects on the human behavior [54,55]. In this case, the body odour cannot be "quantified" in a precisely replicable measure, because it is unique and related to the experimental condition. We speak instead of putative pheromone when the chemical substance related to the social odour is quantified precisely in its dosage and in its chemical composition (e.g., 5 α -Androst-16-en-3 α -ol and Estradiol) [47,49].

Chopra used EEG to record CSERPs, investigating olfactory sensitivity to social odour and sex-related differences during puberty. The results showed that during puberty, male subjects processed bad smells differently from female subjects. Not only were they less sensitive to the odours typically present in axillary sweat, they were also less sensitive to other types of odour. This may be partly due to specific adaptations to odours present in underarm sweat, but it may also reflect hormonal modification of the perception of odours [56]. In our recent work, not yet published, carried out in collaboration with Ishiguro's group, we administered putative pheromones by volatilising them on the object with which the experimental subject interfaces. We showed that, administered in this way, these odourants can produce significant spectral power variations in EEG, and that these variations are gender-dependent [57]. In particular, centroparietal localization presented a social odour effect for both 5 α -Androst-16-en-3 α -ol and Estradiol, which induced a greater presence of alpha and delta waves. Furthermore, delta rhythm highlighted points of co-activity in the right orbitofrontal area, involved in odour recognition memory [58] and social behaviour [59,60], as well as in the left centroparietal site.

Studies such as these show that EEG, which has been used to record responses elicited through the CSERP paradigm, is a valid tool for evaluating how our brain processes olfactory information and how that information is used. For example, Laudien and collaborators [61] investigated whether olfactory processing was influenced by temporary helplessness. Helplessness was induced by asking subjects to solve an insoluble social discrimination test and providing false feedback, in conjunction

with the presentation of two different odourants. At the end of the study, the researchers noted that the effects of helplessness on CSERPs resembled the deviations found in depressed patients, suggesting a general effect of mood [61]. The OERP and CSERP technique has also been used to investigate correlations between a sense of smell, memory, and emotions.

Odours, like flavours, evoke sensations of “pleasantness” and preference, as well as feelings of “unpleasantness” or avoidance, more strongly than other sensory stimuli. Kim and Watanuki [62] analysed the EEG hemispheric lateralisation of pleasant and unpleasant olfactory perceptions elicited by an odour. They showed that positive emotions related to olfaction were associated with activity in the left frontal region, whereas negative emotions related to olfaction were associated with right hemisphere activity. Analysis of the OERP lateralisation also showed that these are generally localised in the left hemisphere, in particular the fronto-parietal area [63].

Numerous EEG studies have investigated the sense of smell in neurodegenerative diseases (e.g., mild cognitive impairment, Alzheimer’s disease), and have shown that olfactory impairment can be considered a biomarker for neurodegenerative processes [64–67]. Moreover, an olfactory impairment can be present also in primary progressive aphasia [68], a specific aspect of a clinical dementia syndrome.

The studies described so far demonstrate that EEG, and in particular, OERPs and CSERPs, can be used to explore the cortical processing of olfactory and trigeminal chemosensory inputs in humans, by recording electrophysiological potentials elicited by chemosensory events.

Furthermore, OERP/CSERP are considered suitable techniques for clinical evaluation, as well as for basic scientific research [69].

2. Magneto-Encephalography and Chemical Perception

MEG is another complex neuroimaging technique used in olfactory paradigms [3,70–73], and offers high temporal and spatial resolution and high data reliability [74,75]. In several studies, MEG has been used to describe the chronological sequence of different stages of processing in different neural substrates in olfactory paradigms [76]. MEG has therefore made possible the study of cortical activity in research aimed to probe the olfactory responses elicited during several olfactive processes or tasks. Walla and collaborators [77] used MEG to investigate the possible influence of an olfactory stimulus on the performance of a word repetition task; the temporal resolution of the technique meant that it was possible to detect that the pattern of activity associated with the processing of words associated with an olfactory stimulus was different from that obtained with words not associated with the olfactory stimulus.

The same researchers investigated the influence of smell on assessments of the intensity and valence of visual stimuli [78], presenting five different categories of images (child, flower, eroticism, fear, and disgust) in five different odour conditions. The subjects’ task was to evaluate the emotional content of each image with respect to valence and intensity; MEG results yielded an interaction between odour and image presentation, highlighting a close cross-modal correlation. In another MEG study, Walla found that in patients with mild cognitive impairment, the interaction between the sense of smell and visually induced emotion occurs mostly below the level of consciousness, and that the effect of a simultaneously presented odour on conscious processing of visual information seems to depend on the type of emotion aroused by the visual stimulus [79].

A further MEG clinical study focused on olfactory processing in Parkinson’s disease [72]. This study confirmed the finding of a previous EEG study [3], showing that olfactory impairment is a biomarker for Parkinson’s disease.

All these MEG studies used an air-dilution olfactometer (OM6b, Burghart, Wedel, Germany) to deliver odours to single nostril, asynchronous to breathing.

3. Chemosensation and the Peripheral Nervous System: Electro-Olfactography, Breath, and Volatile Organic Compounds

The sense of smell seems to be mainly modulated by a breath-dependent sensory gate [65,80]. The olfactory processing begins, in fact, with breathing, and elicits, at first, peripheral neuronal

activations and metabolic responses, followed by complex functional processes of cortical pathways. This process can be studied both centrally through OERPs, and peripherally, through the study of human-exhaled, volatile organic compounds (VOCs). We have already discussed how the CSERPs are the main psychophysiological and electroencephalographic tools used to study olfactory responses, due to the chemical stimulus [15], and how these tools have allowed us to make numerous inferences about olfactory functioning and processing. Further OERP research has been conducted to study the different functionality of the nasal mucosa. In two different studies, in fact, two different groups of researchers, in both of which Hummel was a part, studied the different characteristics of the nasal mucosa during a stimulation phase, in order to detect its functional difference. In a first study [40], the electrophysiological and psychophysical measurements obtained in response to mechanical and chemo-somatosensory stimulation were compared in two different regions of the nasal mucosa, taking a sample of 40 subjects. The results show how the stimulus actually underwent different types of processing, underlining the idea that the respiratory mucosa should not be seen as a homogeneous tissue, but presents different sensitivities to trigeminal stimulation depending on the quality of the stimulus and the stimulation site [40]. In a second study [23], the researchers investigated the differences in the distribution of intranasal trigeminal receptors in humans, using an electrophysiological measure of trigeminal-induced activation—the negative potential of the mucosa [23]. After stimulating the subjects with CO₂, which acts particularly on the trigeminal, lower amplitudes were recorded than the negative potential of the mucosa in the olfactory cleft. These results are compatible with the idea that the trigeminal system acts as a sentinel of human airways.

Speaking of expired VOCs, through numerous studies conducted, we know that in a healthy human condition, the 99% of the exhaled breath matrix is composed of some compounds of inorganic gases, such as nitrogen, oxygen, and carbon dioxide, combined with water vapour and inert gases [52,81,82]. The residual part consists of a mixture of many molecules, referred to as both non-volatile organic compounds (for example, leukotrienes, prostaglandins, and serotonin) and volatile organic compounds (for example, aldehydes, ketones, and benzene derivatives) [81,83]. The mixture of these molecules is called VOCs. The latter are subdivided into exogenous VOCs, when they depend on an external component of human metabolic processes, and endogenous VOCs, when they depend on an internal component of human metabolic processes. As in the case of OERPs, studying VOCs for both diagnostic and research purposes is particularly useful, since the VOC results obtained in the expiration reflect biochemical alterations related to metabolic changes, a possible organ failure, or a neuronal dysfunction in disease states, which are, at least in part, transmitted through the lung to alveolar exhaled breath [82,83]. Because of their reliability, VOC studies have also been applied both to the study of neurodegenerative diseases [84,85] and cognition [86].

Although OERPs and VOCs have been studied and investigated, this has been done only by considering them separately. In fact, until a few years ago, the connection between OERPs and VOCs had not been studied in detail. In recent times, however, Invitto and Mazzatenta [50] have conducted a study aimed at probing the possible connection between OERPs and VOCs in an olfactory research paradigm. In this study, two types of chemical stimulation were investigated (PEA and Vaseline oil) during an OERP and VOC co-recording. The results of the study highlighted a slow but steady connection between OERPs and VOCs, reinforcing the hypothesis that this relationship must be kept in consideration in future research [50].

4. Developmental Olfactory Electroencephalography in Infant Research

What has been described until now refers to the treatment of recording instruments that have been used to study and investigate the olfactory system in the adult.

In recent years, however, some researchers have focused attention on the olfactory mechanisms in developmental EEG [87–89], which is proper for newborns and infants.

Smell, in newborns, is of crucial importance, especially in the first weeks of life where one of the first ties to the mother is established. Several studies have shown that newborns have a good sense of smell. They are able to recognize and discriminate odours, and are able to distinguish the smell of their mothers from others and between human and artificial milk. Furthermore, the sense of smell

allows the prenatal acquisition of perceptual expectations, which the neonatal brain can use to address the novelty of the postnatal environment in which it will find itself involved [90]. However, although the developmental sensory and perceptive parameters of smell are almost equal to those of the mature function (i.e., olfactory discrimination, identification, and olfactory memory), the developmental processes seem to act on the hedonic integration of odours [90–92]. In fact, from the first postnatal week, children rely on this olfactory competence in social contexts: olfactory cues, derived from body chemistry, are used to differentiate between family members or non-family members [92]. Wagner and collaborators, in one of their studies [93], attempted to understand the value of the hedonic response in newborns during the first two years of life. After administering eight different types of odours, the researchers evaluated the results obtained, stating that, during the first two years, children not only succeed in discerning the hedonic value of odours, but in avoiding the unpleasant ones. Therefore, these results highlight both the plasticity of hedonic responses to food odours and the relatively selective avoidance behaviour towards some unpleasant odours [93].

OERPs have not been measured systematically in newborns. Schriever and collaborators, sought to establish an objective method for assessing the olfactory function of newborns, so as to allow an equally objective measurement of OERPs [94]. To do this, the researchers recruited 13 children, with an age range of 23 to 41 days, of which 6 were females and 7 were males. After being examined to exclude any type of obstacle for research, the children were subjected to an odorous task for about 15 min.



Figure 3. Example of an olfactory stimulation during an OERP recording session in an infant. The displayed OERP registration was carried out within the INSPIRE Lab (Vito Fazzi Hospital-Lecce, Italy).

In order to arouse the OERP, the children smelled PEA, a rose-like odour. The results showed that the OERPs were clearly visible in the Fz and Cz electrodes. Specifically, in Cz the OERP was clearly visible, with a positive peak just after 500 ms. However, with regard to the C3, C4, and Pz electrodes, it was noted that not all infants showed evident OERP [94].

With these results, the researchers were able to conclude that OERP can also be detected in newborns, in the same way and in the same way as they are measured in adult subjects. In fact, in the case of the study carried out, OERPs were detectable in 70% of cases, in order with those that would be obtained by testing adult subjects. All this confirms, once again, that the sense of smell in newborns is well developed and can be studied objectively, through studies like the one just described.

Figure 3 shows an example of how an odorous stimulus can be delivered, through a Plexiglas tube, during an infant EEG recording.

A further infant research study was conducted by Sanders to assess the frontal asymmetry elicited by olfactory administration (i.e., lavender or rosemary) [95]. This study revealed that infant EEG was similar to adult EEG behaviour, suggesting that either the lavender or rosemary smell may induce left frontal EEG shifting (not age-related) in subjects that present greater baselines relative to right frontal EEG activation. Schriever and colleagues therefore concluded that the interpretation of

the results, collected in EEG infant research, is difficult, and the main advantage of CSERP and OERP is the high temporal resolution—which, however, is not exploited with the method of time-frequency analysis used by Sanders et al. [94,95].

In conclusion, it is possible to affirm that Schriever and colleagues have, albeit in a preliminary manner, shown that they can objectively study and analyse the OERPs detected in newborns [94].

In particular, the confirmation that these tools can effectively produce reliable and useful results for an objective evaluation, is described by Hummel [96]. The aim of the research was to identify and evaluate the changes in infant olfactory processing, and to probe, at the same time, the electrophysiological correlates. The researchers found that the responses to the different tasks had been differentiated. In particular, thanks to the use of the ERP technique, it has been possible to obtain an even more in-depth framework about the olfactory processes in newborns [96].

We can therefore conclude that even if functional developmental olfactometry is still a new field, and with results still susceptible to further investigation, this method can be applied in this developmental range, because it is this period of the life cycle where the sense of smell has a predominant role, even from the evolutionary point of view.

5. Methodological Limits of Chemical Detection Systems and Devices in Cognitive Neuroscience.

The olfactometer most commonly used in conjunction with EEG was patented by Sedgwick [97]. Sedgwick introduced a task in which the subject is exposed to visual stimulation (with the onset of visual stimulation that is triggered in the EEG track, as normally occurs for EEG perceptual tasks), which is associated or not associated with olfactory stimulation. The CSERP components, elicited by the olfactometer, differed depending on whether the stimulus was visual, olfactory (responses to olfactory stimuli were not investigated by Sedgwick), or cross-modal (i.e., visual and olfactory) [94,98].

In Sedgwick's study, ERPs were recorded over a 1540 ms period, starting 500 ms before the stimulus onset (i.e., the presentation of a new picture). It is important to note that Sedgwick used visual rather than olfactory stimuli. In this classic olfactometry experiment, each trace is labelled according to the type of visual stimulus (linked to the olfactory stimulus) and whether the subject identified the stimulus correctly or not (response identified through the subject's motor reaction time) [4].

In particular, preparation of a motor response causes a readiness potential, which modifies ERP components [99–101].

In Sedgwick's paradigm, the trigger for the ERPs was visual rather than olfactory. The proof of this is that in a no-perfume condition, visual ERP components (due to visual stimuli) were evident; furthermore, the no-perfume condition is not a good control condition, because it is, in effect, a visual stimulation condition, whilst the olfactory condition is actually a cross-modal stimulation condition (visual and olfactory stimuli).

The methodology used to elicit CSERPs can induce bias in EEG components. The previous olfactometers [102] used indirect, olfactory-triggered average visuals, or a blink average indirectly tied, in second-order, to olfactory stimulation.

The new class of olfactometers must cover a method that directly involves the olfactory trigger signal.

The bias-free method could not be related to a motor response (so it is not susceptible to the readiness potential) or linked to a visual or auditory stimulus accompanying the olfactory stimulus (rendering the CSERP effectively cross-modal); this could allow a more simple identification of OERP/CSERP components [50,64,65].

Even the MEG studies described in the MEG section are subject to the limitations associated with the fact that olfactory stimulation seems to be cross-modal, and so it is not possible to observe the effects of olfactory stimulation without any cross-modal effect.

Further development of devices designed to measure exclusively olfactory responses, which also take into consideration the subject's peripheral or metabolic response [50], should eventually provide us with a more detailed picture of what happens at the neurocognitive level after olfactory

stimulation, with or without a trigeminal component. Recent research is increasingly in this direction, and now shows a broad field of study, both clinical and cognitive; we could hypothesize that a new line of research is opening, and it could be called “cognitive neuro-olfactometry”.

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