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Mini Review Article

"Unveiling the Scented Spectrum: A Mini Review of Objective Olfactory Assessment and Event-Related Potentials"

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Keywords
Smell, Evoked potential, Olfaction disorders, Perception, Sensation

Running title- "Olfactory Evaluation: Objective Approaches and Event-Related Potentials"

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Abstract

Objective

The objective of the study is to examine the current state of research and technology related to objective olfactory assessment, highlighting the merits and demerits of the techniques. It aims to specifically explore Olfactory event-related potentials, discussing their potential applications, benefits, drawbacks, and future prospects in the field.

Methods

A five-month narrative review examined English-language articles from PubMed, Scopus, and Google Scholar, critically summarizing titles, abstracts, and full texts, while excluding non-English and methodologically weak studies.

Results

This study provides a detailed investigation into various objective methods utilized and the applicability of OERPs for assessing olfaction. We reviewed key elements, such as techniques, stimulus delivery methods, optimal electrode placement, and waveform analysis.

Conclusion

OERPs offer substantial promise in enhancing the diagnostic accuracy of olfactory dysfunction across various clinical contexts. This thorough review highlights the utility and potential of OERPs in improving the precision and efficacy of olfactory assessments.

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1. Introduction

Olfaction, the sensory modality responsible for detecting and discriminating volatile compounds known as odors or aromas,[1] plays a vital role across various species, aiding survival by facilitating the location and pursuit of food, detecting threats, and identifying foes.[2] While sight is essential for distinguishing objects, the olfactory sense enhances visual perception by adding depth, consistency, and emotion.[3]

This inherent ability is evident from infancy, where even amidst synthetic scents, infants can identify and gravitate toward their mothers' body odors.[4] Moreover, the sense of smell is a crucial indicator of food quality, helps spot damaged food, and alerts individuals to potential environmental threats.[5] Certain odors evoke strong emotions and trigger vivid recollections of associated experiences, impacting psychological and physiological states. [6]

Olfactory dysfunction (OD) varies from complete loss (anosmia) to reduced sensitivity (hyposmia), alongside distorted (parosmia) or false (phantosmia) perceptions of odors. Olfactory dysfunction (OD) arises from various factors, including age, illness, genetics, lifestyle, diet, medical history, treatments, viral exposure, and occupation.[7] Mental health conditions like anxiety and depression can also affect smell perception.[8] OD has also gained attention due to its association with COVID-19.[9–11]

Long-term research on the causes of anosmia and hyposmia has revealed that sinus infections,[12] upper respiratory virus infections,[13] prolonged exposure to toxins,[14] and skull fractures [15] are the most common pathological causes of OD.

In light of these considerations, the availability of dependable techniques for assessing olfactory function is essential. This review seeks to discuss the present state of research and technology concerning objective olfactory assessment and underscore the significance of employing objective assessment techniques in clinical settings. It will specifically delve into

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event-related potentials (ERPs), exploring their potential applications, benefits, drawbacks, and future prospects within the field.

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2. Methods

A narrative review was conducted over five months by searching for English-language articles in the electronic databases PubMed, Scopus, and Google Scholar. In addition, further relevant articles pertinent to this review were retrieved by inspecting the references of the articles that had been searched. Specific keywords were used individually or in combination to aid in retrieving relevant articles. The exclusion criteria were non-English articles, articles with misleading titles, and Studies with unclear methodology and weak study designs. The titles, abstracts and full text of all resulting papers, whenever available, were read and kept for reference, and the findings were critically summarised.

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3. Assessment of Olfaction

Assessment of olfaction can be categorized into two categories:

3.1 Subjective Tests / Psychophysical Tests

Due to their ease of use and excellent reliability compared to self-evaluation, psychophysical olfactory assessment tests are extensively employed.[16] These basic principles underpin psychophysical tests:

3.1.1 Odor Identification Test

UPSIT test (University of Pennsylvania Smell Identification Test)

A preliminary 4-booklet, 40-item version of the UPSIT is used for administration. Each booklet has ten odorants delivered randomly, except for avoiding similar aromas that follow one another.[17,18]

3.1.2 Odor Threshold Test

Finding the lowest concentration of an odorant that the human nose can detect is done using the odor detection threshold methodology. In this technique, an odorant is presented to a panel of trained individuals, and the concentration at which the odor becomes perceptible is determined.[17]

3.1.3 Odor Discrimination Test

Olfactory discrimination tests assess one's ability to differentiate between various odors based on intensity or quality without identifying them. Two stimuli are presented one after the other, and the subject's task is to tell if they smell the same or different. The number of accurate answers determines the test score. The Sniffin' Sticks test is a popular technique for evaluating the olfactory function, particularly odor recognition, threshold & discrimination skills.[19,20]

3.1.4 Odor Intensity Test

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Tests of odor intensity are employed to evaluate how people perceive the relative variations in odor intensity when stimulus energy changes. In these tests, rating methods like category or visual analog scales are frequently used.[17]

Odor-identification tests tailored to various cultural regions have been developed due to the importance of familiarity with specific scents for accurate identification. Notable examples include the Pennsylvania Smell Identification Test (UPSIT), the Connecticut Chemosensory Clinical Research Center (CCCRC) Identification Test in the USA, and the Sniffin' Sticks in Central Europe. The efficacy of these tests is region-specific. Similarly, the Scandinavian Odor Identification Test (SOIT) was developed for the Scandinavian population

The Brief Smell Identification Test (B-SIT) is a streamlined version of the University of Pennsylvania Smell Identification Test (UPSIT) designed to assess olfactory function quickly. It typically includes 12 common odorants encapsulated in scratch-and-sniff format. The test is straightforward to administer, with participants selecting the correct odour from multiple-choice options for each scent. B-SIT is frequently used in clinical environments to screen for smell impairments.[21–23]

The 40-item Monell Extended Sniffin' Sticks Identification Test (MONEX-40) is a valuable tool for evaluating odour identification in research, particularly useful in functional neuroimaging studies with healthy individuals.[24]

3.2 Objective tests

While psychophysical tests have been frequently used over the years due to their affordability, usefulness, effectiveness, and relative reliability, given that the subject's cooperation is required, they are regarded as subjective or semi-objective. These are limited for quantitative assessments,[16,25] rendering them unsuitable for children, patients unable to participate effectively, or in medico-legal contexts where sincere participation cannot be assumed.[26]

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Therefore, researchers have sought objective methods to assess olfactory function, aiming to overcome the limitations mentioned.

3.2.1 PET (Positron emission Tomography) Scan

PET utilizes the $H2^{150}$ bolus to delineate the changes in local cerebral blood flow, which indicates dynamic neural function due to its parallel increase with neural activity. PET imaging offers several advantages, including the simultaneous assessment of neural activity across various brain regions and exceptional visualization of activity in primary and secondary olfactory cortex. However, PET encounters notable limitations in olfaction assessment. These include restricted temporal resolution, which hampers the precise tracking of rapid neural processes involved in olfactory perception, and the exposure to radioactive isotopes, posing potential risks. Furthermore, limited accessibility to PET facilities and spatial resolution challenges, such as discerning closely situated brain foci, impede the accurate depiction of olfactory processing using PET imaging techniques.[27]

3.2.2 fMRI (Functional Magnetic Resonance Imaging)

fMRI measures changes in blood flow linked to neural activity using the BOLD (Blood Oxygen Level Dependant) signal, derived from the ratio of oxyhemoglobin to deoxyhemoglobin. fMRI offers enhanced accessibility and affordability, eliminates radiation exposure concerns, and provides superior spatial and temporal resolution compared to PET. However, susceptibility artifacts in specific brain regions, like the orbitofrontal cortex, and pulsatile artifacts from respiratory motion can compromise its accuracy and reliability in olfaction assessment. Despite efforts to address these limitations by developing various techniques, conclusive evidence supporting their efficacy in olfactory assessment still needs to be uncovered in the scientific literature.[27]

3.2.3 Electro-Olfactography (EOG)

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It involves measuring electrical signals directly from the olfactory epithelium in the nasal cavity in response to olfactory stimuli. EOG recordings detect changes in electrical potential across the olfactory epithelium when odorants bind to olfactory receptor neurons. EOG is often used to study the peripheral aspects of olfaction, such as receptor activation and adaptation, and can provide information about the sensitivity and response properties of olfactory receptor neurons.[28]

3.2.4 Olfactory event-related potentials (OERP)

OERPs are based on the electroencephalography (EEG) recording of brain activity responses to the presentation of an olfactory stimulus using electrodes placed on the scalp. OERP provides distinct advantages in olfactory assessment, correlating directly with neuronal activation and offering high temporal resolution for examining sequential processing. It accommodates subjects with response difficulties (such as children and aphasic patients) and ensures consistency across experimenters, being non-invasive and cost-effective. However, susceptibility to artifacts like blinking and movements necessitates attention maintenance during recording, and careful analysis is required to extract responses from potentially noisy EEG backgrounds.[26,29]

4. Exploring Olfactory Event-Related Potentials: A Primer

OERPs are poly-phasic electric potentials generated in the cortex in response to olfactory stimuli.[30] OERPs arise from the sequential activation of various anatomical structures involved in olfactory processing. The process begins with olfactory sensory input at the olfactory neuroepithelium in the nasal cavities, then progresses through the olfactory nerve and engages with second-order neurons, including the dendrites of mitral and tufted cells within glomeruli in the olfactory bulbs. Post-synaptic fibers from these neurons extend to primary olfactory areas. The piriform cortex establishes connections with the thalamus, hypothalamus, and orbitofrontal cortex, while the entorhinal cortex interfaces with the hippocampus. The thalamus further disseminates connections to secondary olfactory areas, contributing to the complex neural circuitry underlying olfactory perception.[31]

4.1 Delivery of stimulus - Olfactometer

Vanillin (a fragrance similar to roses), hydrogen sulfide (H_2S), or 2-phenyl ethyl alcohol can all be used to activate olfactory afferents selectively.[32] An apparatus capable of delivering chemical stimuli with specific characteristics is required. The apparatus needs to deliver stimuli in a rectangular form, guaranteeing swift onset and precise control over timing, duration, and intensity while preventing simultaneous engagement of other sensory systems apart from olfaction. Currently, the Burghart olfactometer is widely utilized for this purpose. This apparatus enables the delivery of stimuli within a continuously flowing stream of air, seamlessly transitioning from odorless to odorized air without detection by participants. By administering humidified and warmed intranasal airflow, subjects adapt quickly to the continuous airflow, minimizing perceived discomfort or awareness of the stimulus delivery process.

With the help of this instrument, control air (C) and odorized diluted (O+D) air is delivered into the nostril. Two separate inlets for control air and odorized diluted air are directed toward the outlet and delivered directly into the subject's nostrils. Two other tubes are present, one of which serves as a valve, and the other is connected to a vacuum line. During stimulus, D+O has to reach the outlet, so C is directed to the vacuum line, and during the Interstimulus interval, D+O is directed to the vacuum line; thus, C reaches the Nostril, as represented in **Figure 1**. There is a fast switch between C and D+O such that the participants are unaware of the control air, and the transition occurs without mechanical or thermal changes.[33–36]

4.2 Electrode placement

Three scalp electrodes in the position Fz, Cz, and Pz were used to record the EEG according to the International 10-20 electrode system. The ground was put on the forehead, and the reference electrode was positioned on the earlobes A1 and A2.[36–40] C3 and C4 were also used in some studies.[26,41]

An electrode above the right eyebrow recorded eye movements and blinks, a technique known as an electrooculogram. Blink artifacts were monitored from an additional site, Fp2.[26] Additional muscular artifacts are discarded if observed. Artifact-free EEG epochs were averaged to get the OERPs.[36]

4.3 Waveforms of OERP

The OERPs are characterized by a prominent negative component denoted as N1, succeeded by a substantial positive component referred to as P2. P1 and N2, among other components, are frequently imperceptible.[35,42,43]

4.3.1 N1 and N2 Component

Changes in stimulus level and intensity determine the amplitude of the N1 component, an early OERP component regulated by both endogenous and external influences. Although the N1 amplitude in the olfactory modality is not concentration-dependent, its latency does decrease

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as odor concentration rises. The stimulus characteristics and the individuals' psychological states are reflected in the N1.

The OERP equivalent of the olfactory mismatch negativity is a negative deflection N2 that occurs 500–600 ms after the N1 component. The deflection is most significant in the parietal midline electrode, suggesting a particular topographical distribution in response to smells.[44]

4.3.2 P1 and P2 Component

The external cortical activity connected to fundamental sensory processing and sensory input detection is reflected in the early OERP components (N1 and P1). Conversely, the P2 and other subsequent OERP components show endogenous cortical activity associated with secondary cognitive processes. P2 latency has attained a reasonable degree of dependability and is measured between 530 and 800 ms following the start of the stimulus.[36,42,45] Maximum amplitudes of the N1 and P2 components are observed over the Cz and Pz positions.

4.3.3 P3 Component

P3 is an "attention"-related component,[46] a late positive complex in the OERP that represents psychological processes of processing information from stimuli. These processes are impacted by subjective stimulus probability and stimulus meaning, which are linked to emotional and cognitive processes.[44] The representative waveforms are shown in **Figure 2**.

Not the latency, but the amplitude of the OERP represents the amount of odour. The stimulus's concentration determines the time constant at which the OERP's amplitude decays or adapts.[46]

4.4 Parameters of OERP

The primary parameters governing the OERP components are latency and amplitude.

Latency: The duration between the stimulus's onset and the component's peak, or maximum value.

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Topography: The location on the cranial surface at which the component's highest amplitude can be recorded, enabling the determination of the cortical area that is active in response to a given stimulus.

Amplitude: The vertical distance from the most significant peak to the baseline [30].

4.5 Applications of OERP

4.5.1 Aging

As a method for examining how odor is processed throughout life, the OERP seems to be considerably entrancing. Interpreting specific psychophysical tasks in older adults and children may be limited by subject bias, researcher effects, and criterion alterations.[47] The OERP olfactory assessment may be a more accurate indicator of the aging-related impairment in olfactory processing.[40] It was found that young adults produce larger amplitudes and shorter latencies compared to older individuals.[38,40,47]

4.5.2 Gender differences

OERP amplitudes and latencies in response to olfactory stimuli are correlated with age, sex, stimulus concentration, and Interstimulus interval.[38,48] The OERP can provide important information, such as differences in the OERP related to gender and age, that cannot be discovered using other olfactory tests.[38] Compared to men, women have shown greater sensitivity and lower thresholds to OERP.[40]

Women exhibited more prominent early components (P1, N1) in the signal-to-noise ratio of individual OERP averages compared to men. Additionally, late positive components (P2/P3) displayed larger amplitudes and shorter latencies in women as opposed to men. These findings imply that gender differences in olfactory processing may primarily stem from heightened levels of brain processing.[43,49] Some researchers have suggested that sex-specific variations exist in the sensory processing of olfactory stimuli. Specifically, women tend to exhibit larger

amplitudes and longer latencies in their left hemisphere responses, whereas men show a comparable pattern in their right hemispheres when exposed to identical stimuli.[45]

Compared to men, women's P3 amplitudes were higher when they attended but not when they ignored amyl acetate stimuli. Because the P3 component is a sign of higher cognitive processing,[44,50] this led to the theory that men and women differ in cognitive measures of chemosensory processing.[51]

In the current scientific literature, limited OERP studies are specifically designed to investigate sex differences in olfaction. These studies would contribute valuable insights into the neurophysiological underpinnings of olfaction, facilitating a more nuanced comprehension of sensory perception.

4.5.3 Diagnostic in Neurodegenerative Diseases

Olfactory dysfunctions have garnered significant attention due to their potential link to the development of idiopathic Parkinson's disease (IPD) and Alzheimer's disease (AD).[52,53]

4.5.3.1 Parkinson's Disease

Because olfactory function clinical assessments are affordable and relatively simple, olfaction is a desirable biomarker for Parkinson's disease, including prognosis, pre-motor diagnostics, and differential diagnosis.[54,55] In general, olfactory testing could be helpful in distinguishing tauopathies (Progressive Supranuclear palsy (PSP) and Corticobasal degeneration (CBD)) and non-degenerative forms of parkinsonism (Normal pressure hydrocephalus (NPH), Drug-induced Parkinsonism (DIP), vascular parkinsonism, and Essential tremor (ET)) from idiopathic Parkinson's disease. The olfactory function measured by OERP revealed elevated latency but unaltered amplitude in PD patients.[33,56]

4.5.3.2 Alzheimer's disease

The degree and course of AD can be clinically identified by olfactory function.[52,54,57–63] Olfactory function assessment is a low-cost, non-invasive method with low expert

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interpretation and administration requirements and a sensitive measure for early AD detection.[64–66] OERPs play a pivotal role in facilitating early diagnosis and prognostication of Alzheimer's disease. There has been observed augmentation in the latency of distinct components within OERP in Apolipoprotein ε4 positive individuals, which are implicated in AD.[67–69] The highest genetic risk factor for the late-onset familial and sporadic forms of AD is the ApoE ε4 allele.[70,71] When used in tandem, ApoE ε4 genetic testing and OERPs may improve risk assessment accuracy and lead to detection far earlier than other cognitive impairment symptoms manifest.[69]

4.5.3.3 Multiple Sclerosis (MS)

MS patients exhibit varying degrees of olfactory impairment,[72,73] and it has been found that a direct relationship exists between olfactory dysfunction, degree of disability, and length of disease based on OERP.[36,74–76]

We cannot completely rule out the idea that olfactory function assessed at the outset of MS may be predictive of the course of the disease, as seen in the cases of Parkinson's and Alzheimer's disease. Nevertheless, longitudinal research will be necessary to validate the theory and investigate the function of olfaction as a disease sign in multiple sclerosis.[74,77]

4.5.4 OERPs in IONM (Intraoperative Neuromonitoring)

Chemical stimulation is typically used to evaluate OERP, but this method is unreliable during surgery because odorants attached to the olfactory mucosa have a long and unpredictable washout period. Ishimaru et al. introduced a method involving electrical stimulation of the olfactory mucosa to acquire olfactory OERPs, utilizing surface electrodes positioned bilaterally on the lateral and frontal sectors of the head.[78] Nonetheless, this intraoperative technique is hindered by the limitation that it is not universally applicable in various craniotomy approaches, with the exception of midsagittal incisions, due to potential local interference during surgical procedures. Additionally, reliance on electrical OERPs implies an assumption

that olfactory dysfunction is contingent upon damage within a specific pathway, thereby underscoring the superiority of utilizing OERP as a more effective tool in outpatient settings.[79] A dependable OERP within the surgical setting would prove invaluable for assessing the integrity of the olfactory pathway and mitigating iatrogenic neurologic deficit. In a study by Sato et al.,[80] OERPs were detected in patients undergoing frontotemporal or bifrontal craniotomies in response to electrical stimulation of the mucosa. Despite their failure to disclose any postoperative anosmia or changes to the OERPs during the case, it's unclear what alarm parameters were applied to notify the surgeon in order to stop a potential neurologic deficiency.[81] Following ASNM guidelines, the criteria of a 50% amplitude change and a 10% latency change, commonly employed in other modalities,[82] could also be considered in this context following thorough research. In a study by Momijian et al., OERP was acquired intraoperatively during general anesthesia and was successfully recorded in 5 out of 8 patients undergoing neurosurgery to excise brain lesions.[83]

Challenges with the current olfactometer include lengthy stimulus averaging, complex technical setup, large size, and noise levels unsuitable for controlled environments like operating rooms. Rigid tubing may hinder precise stimulus delivery. The signal-to-noise ratio and habituation effects need improvement for reliable measurements. Real-time statistical analysis integration is required for prompt detection of changes and timely intervention in clinical settings.[83]

Contemplating these aspects necessitates further investigation to enhance OERP as an improved intraoperative neuromonitoring tool, with the aim of preventing potential disruptions to olfactory function during surgical interventions.

Summary

- Olfaction is essential for human perception, and dysfunction can severely impact survival.
- Subjective psychophysical tests are available, but objective tests are preferred despite certain limitations.
- OERPs are non-invasive and safe, providing valuable insights into age and gender differences in olfactory processing, with women showing greater sensitivity and distinct signal components.
- OERPs are crucial in diagnosing Parkinson's and Alzheimer's diseases by identifying specific olfactory impairments, aiding in early detection and prognosis.
- Although promising for assessing olfactory pathways during surgery, current OERP methods face technical challenges, such as lengthy averaging times and complex setups, necessitating further development for reliable intraoperative use.

5. Conclusion

This paper provides an overview of various olfaction assessment methods, with particular attention to the emerging objective test Olfactory Event-Related Potentials. OERP shows promise in addressing the limitations of psychophysical tests by offering broader applicability across diverse populations. It shows potential as an early indicator and prognostic marker for neurodegenerative diseases. Despite notable progress, additional advancements and refinements are required to meet clinical and diagnostic standards.

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Conflict of interests

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Author's contribution

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Multimedia and supplementary material

There is no multimedia or supplementary material.

Data availability statement

No new data were generated or analyzed in support of this research.

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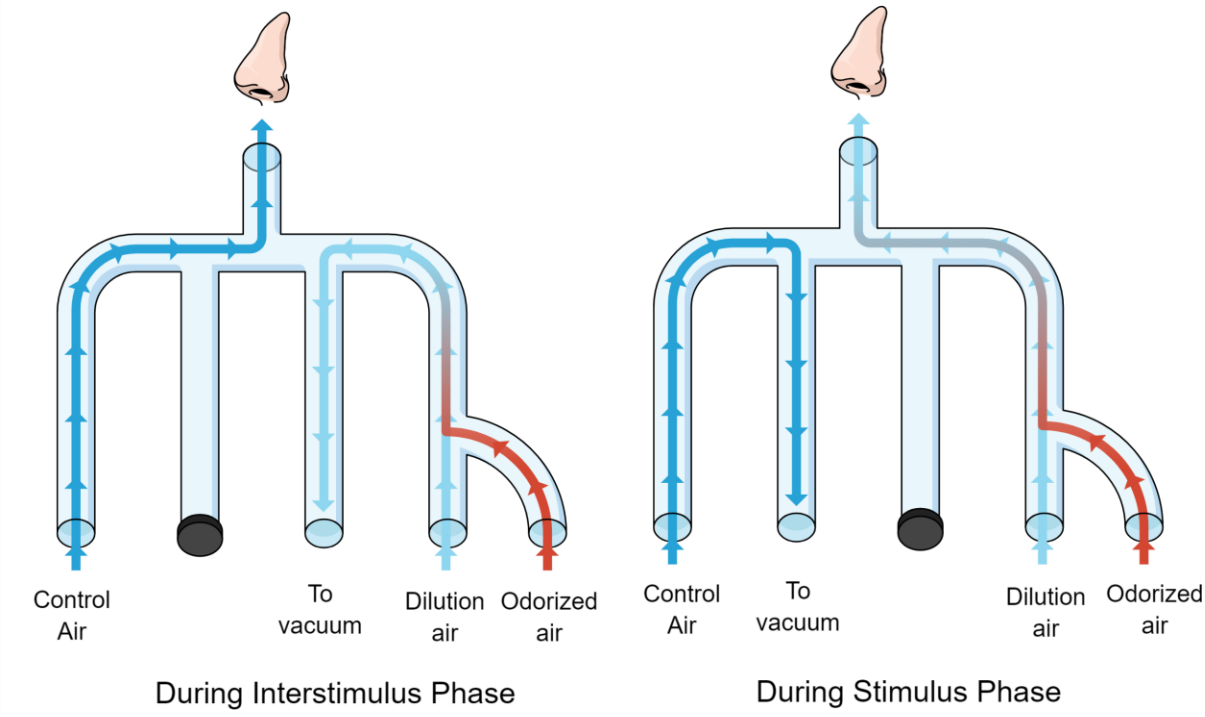

Figure 1

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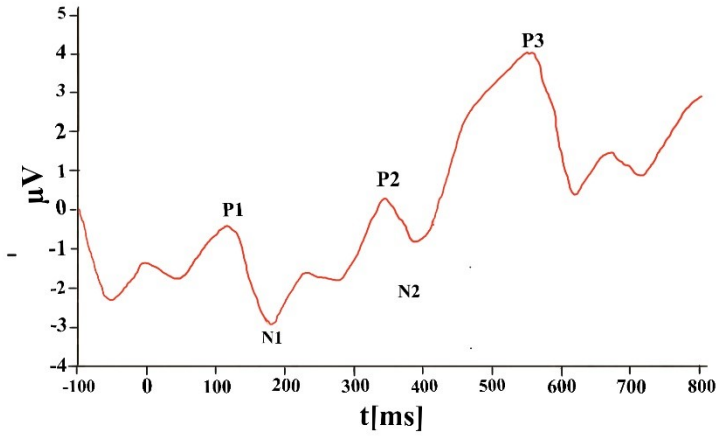

Figure 2

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