46. The Intranasal Trigeminal System

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The trigeminal nerve is the fifth and thickest cranial nerve and not only it is responsible for facial sensation and motor functioning, but it is also responsible for chemosensory perception. On top of innervating the skin of the face, the trigeminal nerve also innervates the mucosa of the nose and mouth. Here, chemosensory perception starts with the activation of different receptors, the most important and best known ones being the transient receptor potential (TRP) channels which give rise to sensations such as burning, warmth, coolness, coldness, and pain. From the mucosa, the trigeminal chemosensory information is conveyed through the trigeminal ganglion to the thalamic nuclei in the brain stem; from here fibers project to both, the somatosensory cortex and chemosensory areas of the brain.

Most odors stimulate the trigeminal system, in addition to the olfactory system, especially in higher concentrations. However, overlaps between both sensory systems are not limited to the stimulus level, as they interact with each other on peripheral (mucosa) and central (brain) levels. As a consequence, subjects with a lacking olfactory system show lower trigeminal sensitivity and subjects with a lack of trigeminal sensitivity show lower olfactory activations.

Different techniques are available to assess the state and the functionality of the trigeminal system. Such techniques include behavioral assessment by testing participants lacking a sense of smell – in order to exclude olfactory interference – as well as administrating different types of stimuli (pure odorants, pure trigeminal, or a mix of both). More objective measures include electrophysiological methods that evaluate the peripheral and central activations via the negative mucosal po-

tentials (NMPs) and the trigeminal event-related potentials (ERPs), respectively, as well as functional magnetic resonance imaging, and to a lesser extent, positron emission tomography (PET).

The trigeminal nerve is responsible for facial sensations (touch and pain) and to a considerably lesser degree to motor functioning (masticating). In addition, it also provides chemosensory information from the oral and nasal mucosa, such as the perception of piquancy when eating something spicy. Although a limited amount of

research has focused on the chemosensory part of the trigeminal system, this chapter aims at providing an overview over key knowledge on the trigeminal system. Specifically, the anatomy, the different pathways, the various methods of studying the system, the interactions between the olfactory and the trigeminal system as well as the impact of the loss of one system on the other are discussed.

46.1 General Neuroanatomy of the Trigeminal System

The trigeminal nerve is the fifth cranial nerve (CN V). It is the largest of the 12 cranial nerves; its name stems from the fact that it has three major branches (tri = three; geminus = twin; hence triplets). These three branches are the ophthalmic nerve (CN V1), the maxillary nerve (CN V2), and the mandibulary nerve (CN V3). The trigeminal nerve is primarily a sensory nerve with some motor functions.

46.1.1 Trigeminal Ganglion, Trigeminal Nuclei

Sensory information from the three branches converges on the trigeminal ganglion (Gasserian ganglion, semilunar ganglion); here, the cell bodies of the incoming

Fig. 46.1 The trigeminal pathway. A: Fibers of the trigeminal nerve (neurons) are located throughout the epithelium of the nasal cavity (*gray*). B: Cell bodies of the trigeminal neuron are located in the trigeminal ganglion. Nevertheless, no information is transferred between neurons at this stage. C: The first (1) relay station is located in the brainstem (*blue*). D: The second (2) relay station is located in the thalamus (*green*). E: Third-order neurons (3) project from the thalamus to the somatosensory regions of the cortex (*orange*). Note that somatotopic information is preserved throughout the pathway. *Purple*: cerebellum; *light orange*: corpus callosum

sensory fibers are located. The trigeminal ganglion has analogous features as the dorsal root ganglia of the spinal cord. Although the cell bodies of the neurons are located in the trigeminal ganglion, there are no synapses; thus the neurons are called pseudo-unipolar. Somatotopic information from the three branches is preserved [46.1], which means that the relative location of the three branches maintains the same location within the trigeminal ganglion. To illustrate, the branches from the ophthalmic nerve will be placed above the branches from the mandibular nerve as their layout on the human face. From here, afferent fibers enter the brain stem in the angle between pons and the middle cerebellar peduncle [46.2]. In the brain stem, they travel to the trigeminal nuclei, which are arranged from the mesencephalon (mesencephalic nucleus) to pons (main sensory trigeminal nucleus) and the rostral portions of the spinal cord (spinal trigeminal nuclei). It is important to note that the fibers are still arranged somatotopically [46.3]. See Fig. 46.1 for an overview over the trigeminal pathway.
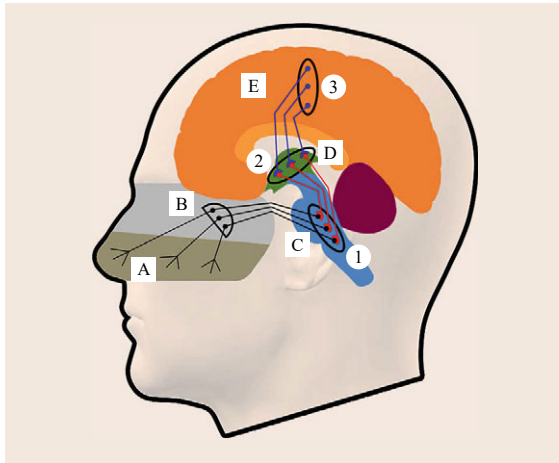
46.1.2 Central Nervous Processing Structures

The first synaptic relay is found in the trigeminal nucleus, a structure located in the brainstem. Here the information is transmitted to neurons projecting to the second relay station in the thalamus which is a regulator for consciousness and alertness. Specifically, trigeminal information travels to lateral (ventrobasal) and central (centromedial and parafascicular) thalamic nuclei. From here, the third neuronal projection sends the information mainly to the somatosensory cortex which represents the brain area responsible for sensations, such as touch, pain, or heat. In humans, the ophthalmic regions are represented in the inferior portion of the postcentral gyrus, whereas information from the mandibular nerve is processed in more superior regions in the central sulcus [46.4, 5]. Consequently, the relative layout of the three trigeminal branches is preserved in all portions of the trigeminal pathway, from the trigeminal ganglion to the somatosensory cortex.

46.2 Chemosensory Trigeminal Neuroanatomy

In addition to the facial skin, different branches of CN V innervate the mucosa of nose and mouth. Specifically, the ethmoidal nerves from the ophtalmic nerve and the nasal and some alveolar branches from the maxillary nerve innervate the nasal mucosa; further, other branches of the maxillary nerve innervate the oral mucosa together with the lingual nerve, the buccal nerve, and the alveolar nerves from the mandibular nerve. In the mucosa, the nerve endings of the trigeminal nerve are capable to detect chemosensory information in addition to somatosensory information, via specific chemoreceptors.

46.2.1 Peripheral Structures, Receptors

On receptor levels, chemical stimuli activate specific receptors of the trigeminal nerve, most of them being ion channels belonging to the subfamily of transient receptor potential (TRP) receptors, which have been discovered only relatively recently and are discussed in detail in Chap. 34 of this book. One of their main characteristics is that they are activated by both, a certain temperature range and chemical stimuli, such as capsaicin, menthol, camphor, and many more.

In addition to the TRP channels, there is also evidence for non-TRP receptors. These receptors are activated by nicotine (nicotinic acetylcholine receptors) [46.6] and acids (proton-gated ion channels) [46.7–10]. Further, in addition to these receptors on free trigeminal nerve endings solitary chemoreceptor cells have been described in the nasal cavity, although not yet in humans [46.11]. These cells are activated by bitter substances via specific receptors and reach the surface of the nasal epithelium and form synaptic contacts with trigeminal afferent nerve fibers. They may add to the repertoire of compounds that can activate the intranasal trigeminal system.

46.2.2 Central Nervous Processing Structures

Chemosensory information shares the processing units with this classical somatosensory pathway. However, chemosensory trigeminal stimuli activate brain regions in addition to these somatosensory structures such as the insula, the orbitofrontal cortex, and the piriform cortex [46.12–14]. Usually, these additional areas are considered being olfactory and gustatory regions. In order to include trigeminal processing, the term *chemosensory areas* has been put forward to describe the ensemble of these regions. While most trigeminal stimuli also evoke odorous sensations, that is, have a smell [46.15], it is unclear whether the activation of the chemosensory areas occurs via the olfactory pathway – stimulation of olfactory receptors by the trigeminal stimulus leads to the activation of olfactory nerves – or whether there is a direct and chemosensory-specific connection between the somatosensory pathway and the chemosensory processing areas, with a hitherto unknown exact neuroanatomy. The latter hypothesis is supported by the fact that even the odorless trigeminal stimulus carbon dioxide leads to the activation of chemosensory brain areas [46.12]. In fact, there are some collaterals of the trigeminal nerve that end within the olfactory epithelium; some even re-enter the central nervous system and terminate within the olfactory bulb [46.16]. While the exact function of these fibers is unclear, they may provide one of the links by which the trigeminal and the olfactory system interact.

46.3 Trigeminal Perception

Compared to the olfactory nerve, chemoreception within the trigeminal system is relatively unspecific. Still, the sensations arising from trigeminal chemosensation are well beyond simple pain perception as trigeminal stimulation may lead to such diverse perceptions as cooling, burning, stinging, or tingling. The TRP channel receptors play a key role in trigeminal perception.

46.3.1 Receptors and Perception

The first TRP receptor to be discovered and described in detail is the TRPV1 receptor. It is activated by noxious heat above 43 °C [46.17] as well as a variety of chemical stimuli, including capsaicin (the spicy ingredient of hot peppers) [46.17], eugenol (the key compound of essential oil of cloves) [46.36], and acids [46.33]. Stimulation of TRPV1 receptors leads to the perception of a tingling perception, which in higher intensities becomes sharp, burning, and painful [46.44]. There are several other TRPV such as TRPV3. This receptor is activated at lower temperatures starting from 39 °C [46.45, 46]. This receptor is also chemosensitive as different compounds, such as thymol (a main component of spices such as oregano and thyme) [46.24, 26], act as agonists. Activation of TRPV3 is associated with the sensation of warmth [46.26].

Table 46.1 Different stimuli activate different TRP receptors

Substance	Receptor	Reference
Acetylcholine		[46.17]
Adenosine triphosphate		[46.17]
Amyl actetate		[46.18, 19]
Allicin		[46.20–22]
Benzaldehyde		[46.18, 19, 23]
Borneol		[46.24]
Bradykinin		[46.17, 25]
6-tert-Butyl-m-cresol		[46.24]
Camphor		[46.24, 26–32]
Cannabinoids		[46.21, 33, 34]
Capsaicin		[46.17, 19, 26, 33]
Capsazepin		[46.17]
Carvacrol		[46.24, 26]
Carveol		[46.24]
L-Carvone		[46.25]
Cinnamaldehyde		[46.25, 28]
Citral		[46.35]
Diallylsulfide		[46.20]
Dihydrocarveol		[46.24]
Eucalyptol		[46.27, 31]
Eugenol		[46.23, 25, 26, 36]
Formalin		[46.21, 37, 38]
Geranial		[46.35]
Geraniol		[46.35, 39]
Gingerol		[46.25]
Glutamate		[46.17]
HC-030031		[46.37]
Helional		[46.39]
Heliotropyl acetone		[46.39]
cyclo-Hexanol		[46.27]
cyclo-Hexanone		[46.19, 23]

Table 46.1 (continued)

Substance	Receptor	Reference
Histamine		[46.17]
4-Hydroxynonenal		[46.21, 38, 40]
Hypertonic saline		[46.17]
Icilin		[46.27]
Incensol acetate		[46.41]
Isopulegol		[46.25]
Javanol		[46.39]
Limonene		[46.19]
cis-p-Menthane-3,8-diol		[46.25]
trans-p-Menthane-3,8-diol		[46.25]
Menthol		[46.25, 27, 28, 42]
Menthone		[46.27]
Menthyl lactate		[46.25]
Methyl salicylate		[46.25]
Mustard oil		[46.25, 33, 37]
Neral		[46.35]
Nerol		[46.35]
(−)-Nicotine		[46.19]
Phenyl ethanol		[46.39]
Putrescine		[46.43]
Protons		[46.17]
Resiniferatoxin		[46.17]
Sandalore		[46.39]
Sandranol		[46.39]
Serotonin		[46.17]
Substance P		[46.17]
Spermidine		[46.43]
Spermine		[46.43]
Terpineol		[46.18]
Toluene		[46.18, 19]
Thymol		[46.24, 26]

Table 46.1 (continued)

Substance	Receptor	
Vanillin	■ ■ ■	[46.39]
WS23	■	[46.25]
WS3	■	[46.25]

Dark blue: TRPA1; *light blue*: TRPM8; *orange*: TRPV3; *red*: TRPV1; *full square*: agonist; *black diagonal stripes*: antagonist; *white diagonal stripes*: partial agonist; *empty square*: no effect; *empty space*: not tested

Fig. 46.2 Receptive range of four intranasal TRP receptors. The *green area* indicates the physiological temperature in the nasopharynx, that is, the temperature to which the nose conditions the inhaled air (after [46.49])

On the other side of the physiological temperature range, we find the TRPM8 receptor. This particular receptor is activated by cool temperatures starting from 39 °C [46.27], as well as chemical substances such as menthol (main component of peppermint) [46.27], and eucalyptol (eucalyptus) [46.47]. Stimulation of this receptor provides the sensation of cooling without being particularly painful. Further toward the range of noxious cold is the TRPA1 channel, which is activated by cold temperatures below 17 °C [46.25, 33]. Again, this receptor is chemosensitive as compounds such as allyl thioisocyanate (mustard oil) [46.25, 33] serve as agonists. TRPA1 stimulation gives rise to a dull, painful sensation. See Fig. 46.2 for an overview over the temperature ranges of these four receptors. It is interesting to note that many of the stimuli are ingredients of spices and herbs, such as hot pepper, cloves, oregano, thyme, eucalyptus, peppermint, mustard, etc. See Table 46.1 for an overview of the different stimuli that activate the four TRP receptors mentioned in this chapter.

When humans breathe air at room temperature normally, inhaled air is heated within the nasal cavity to an average of 28−32 °C [46.48, 49]. This temperature lies between the temperature ranges of TRPM8/TRPA1 on one hand and TRPV3/TRPV1 on the other hand. Thus, none of these receptors should be activated when we breathe clean air at room temperature. Upon stronger inhalation of air at room temperature, however, the TRPM8 receptor may be activated, since intranasal temperature drops [46.49]. Further, changes of the air temperature induce receptor potentials and, as a consequence, the perception of cold, cool, warm, or hot. Similarly, the presence of one of the multiple trigeminal stimuli may induce receptor potentials evoking according sensations even in the absence of a real temperature change. In fact, the inhalation of menthol does lead to the perception of coolness and, by analogy, the sensation of an increased nasal patency. Objective measures of nasal air temperature and nasal patency however show that menthol inhalations do not affect any of both measures [46.48].

We do not yet know how different trigeminal receptors are distributed within the nasal epithelium. In this context, it is interesting to note that three different trigeminal stimuli, which most likely bind to different receptors, evoked comparable activation patterns at different sites within the nasal epithelium [46.50]. Therefore, different areas of the nasal cavity seem to exhibit distinct concentrations of receptors, but the ratios between different receptors seem to be stable throughout the nasal cavity.

46.4 Assessment of the Trigeminal System

Different methods are available to assess the sensitivity of trigeminal system in humans in vivo. One challenge a researcher faces is the fact that olfactory and trigeminal system are intimately related. Specifically, most trigeminal stimuli activate the olfactory system in addition to the trigeminal system, and they do so at lower concentrations [46.51]. Therefore, although the intensity of the trigeminal sensation is usually stronger than the olfactory one, there usually is some form of interference from the olfactory input. Several methods have been used to overcome this problem, each of which has its own advantages and disadvantages.

46.4.1 Behavioral Methods

Different methods are available to assess sensitivity in the trigeminal system with behavioral measures. In order to avoid the effects of olfactory interference, one could either test participants with anosmia, i. e., lack of

olfactory perceptions, or focus on tests which rely more or less exclusively on trigeminal sensations.

Behavioral Testing in Anosmia

Anosmia, acquired or congenital lack of olfactory function is a relatively common finding as 1 in 20 is affected in the general population [46.52, 53]. Of course, persons with anosmia do not perceive the olfactory component of mixed olfactory-trigeminal stimuli; thus minimizing olfactory interference. In fact, persons with anosmia can only detect mixed olfactory-trigeminal stimuli by virtue of the test compound's trigeminal component. This can be used to assess the trigeminal impact of a substance, since the percentage of subjects with anosmia who detect a stimulus is correlated with the stimulus' trigeminal impact [46.15, 54]. The typical method to assess olfactory thresholds in persons with normal olfactory function is to ask participants to detect an odorous substance in different concentrations amongst several odorless blanks. If the same stimulus with the same paradigm is used in subjects with anosmia the resulting threshold will be based on the trigeminal sensation [46.55, 56], thus providing a method to assess trigeminal thresholds.

However, one has to be careful when generalizing the findings from persons with anosmia to the general population. We know that anosmia is associated with a reduced trigeminal sensitivity [46.57–60]. The difference in trigeminal sensitivity between subjects with anosmia and participants with a normal sense of smell may be small, and therefore not be detected when investigating only a small number of subjects [46.55, 56, 61], but is a clear limiting factor of this approach.

Tests Depending on Trigeminal Stimulation

In addition to testing subjects who cannot perceive olfactory information, olfactory interference can be excluded in those tests, which depend solely on trigeminal perception. One exemplary method is the lateralization task, in which subjects are asked to identify the nostril to which a stimulus has been delivered (lateralization task). This task is based on the fact that humans are unable to localize pure odorants [46.62, 63], but can do so for stimuli which activate the trigeminal system, mixed olfactory/trigeminal stimuli. Depending on the trigeminal impact [46.44], such stimuli can be localized with high accuracy [46.51, 62, 64–67]. Using this fact allows for two different tasks: first, one can determine the sensitivity of the trigeminal system in a given population or compare sensitivity between two groups of subjects [46.66, 68]; second, one can determine the trigeminal potency of different chemical compounds [46.44, 56]. Thus, by using the lateralization test, one can determine the threshold for a given substance, by using

a staircase procedure [46.51]. Such a procedure is often used as an experimental design to assess the thresholds by lowering or elevating the task difficulty until we find the minimally intense stimuli to which the participant would respond accurately. Alternatively, a single concentration of a test compound with strong trigeminal impact may be used in a semiquantitative screening protocol. Here, the sum of correct identifications is used for further statistical analyses. The latter is mostly used in a clinical setting. The lateralization test can be cumbersome, since it is important to keep a relatively long inter stimulus interval of at least 40 s in order to avoid habituation [46.69]. An alternative method is to register response times in a lateralization task [46.70], which has the advantage to provide parametric data with fewer trials and thus shorter test times.

As an alternative, some groups take advantage of the fact that the cornea and conjunctiva of the eye are also innervated by the trigeminal nerve. These epithelia, in fact, allow for the perception of painful sensations, but do not respond to pure olfactory stimuli. Thus, vapor-phase chemical stimuli which evoke the sensations of burning or stinging in the cornea can be used to assess trigeminal irritation thresholds in the eye. However, one has to be careful to avoid co-stimulation of the nose and thus the olfactory system. Corneal thresholds can be used as estimates of trigeminal sensitivity since irritation thresholds obtained in the eye and nose are significantly correlated [46.71].

Another approach is to instruct subjects with a normal olfactory function to distinguish between olfactory and trigeminal sensations. Therefore, after being trained to focus on trigeminal sensations subjects learn to disregard the simultaneous olfactory sensation. Typically, subjects receive instructions such as *have you felt any sensation like burning, stinging, cooling, or tickling?* By using this method, one can assess trigeminal perception thresholds [46.58, 72–74]. However, one has to keep in mind that olfactory interference will occur and can unconsciously affect subjects' responses, which limits the application of this method.

Another method rules out olfactory interference, by using *pure* trigeminal stimuli, stimuli which exclusively activate the trigeminal system. However, a possible concomitant olfactory stimulation is very difficult to exclude. Only few stimuli are available in this category; they include CO_2 or capsaicin. Here it is important to note that CO_2 acts as a trigeminal stimulus only in very high concentrations ($> 100\,000$ ppm) [46.75], which may be dangerous for participants' safety. Thus, CO_2 as a nasal trigeminal stimulus can safely be employed only as brief (< 3 s) stimulus, or alternatively with mouth breathing and velopalatine closure (isolation of the nasal cavity).

46.4.2 Electrophysiological Methods

In contrast to behavioral techniques, electrophysiological measures rely less on participants' response and collaboration. They therefore provide a more objective assessment of trigeminal sensitivity. Still, the problem of olfactory interference is difficult to avoid.

Event–Related Potentials

Trigeminal ERP are electroencephalography (EEG)-derived polyphasic signals obtained at the surface of the scalp [46.76] due to the activation of cortical neurons that generate electromagnetic fields. In other words, trigeminal ERP are a central nervous representation of the processing of trigeminally mediated sensations. The EEG is a noisy signal containing activity from many cortical neurons; therefore ERP have to be extracted from the background activity; this can be done by averaging responses to single stimuli reducing the random background noise [46.77]. Again, single stimulations have to be separated by a relatively long inter-stimulus interval of at least $30-40$ s to avoid effects of habituation [46.69]. Further, in order to obtain meaningful averages with an acceptable signal-to-noise ratio, at least 10 single responses have to be recorded resulting in ERP sessions of 45 min to 2 h. This requires subjects' vigilance to be stabilized by simple tasks, such as a tracking task on a computer screen [46.78]. The main advantage of ERP is the very high temporal resolution in the range of milliseconds. However, this comes with a relatively poor spatial resolution. Further, ERP are prone to artifacts; therefore successful ERP recording requires an olfactometer, a device which allows for the delivery of stimuli with:

1. A sharp onset
2. Exactly defined duration
3. Without concomitant mechanical co-stimulation
4. Without concomitant thermal co-stimulation [46.76].

The nomenclature of the trigeminal ERP responses follows that of other sensory domains; a small first positive peak (P1) typically occurs at latencies later than 200 ms, followed by a first major negative peak (N1; approximately 400 ms), and the late positive complex (P2 or P2/P3; approximately 650 ms) [46.77, 78] (Fig. 46.3 for an overview). Largest responses are obtained from central and parietal electrodes; measures of interest are usually amplitudes and latencies of the major peaks. ERP are mostly used in a research setting, since they require a relatively high effort in terms of cost and time. Further, the discussion on olfactory interference also applies to trigeminal ERP: since most trigeminal stimuli also activate the olfactory system, trigeminal ERP
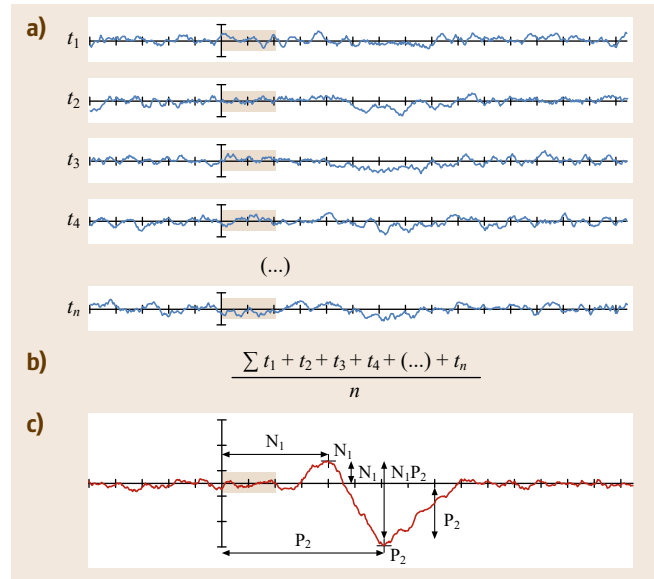
Fig. 46.3a–c Procedure of trigeminal ERP recording: **(a)** Single EEG recordings in response to a 200 ms stimulus (*shaded area* indicates stimulus). Note that response to the stimulus is overlapped by random brain activity. In order to extract specific response, several trials are recorded (t_1 to t_n). **(b)** EEG response are averaged. **(c)** Event-related potential is visible after averaging. The most important peaks, N1 and P2 are indicated by *crosshair*. For each peak one can analyze latency (*blue*; N1 and P2), and amplitude (*red*; baseline to peak amplitude: N1 and P2; peak-to-peak amplitude: N1P2)

will in most cases also contain signals from olfactory processing areas.

Negative Mucosal Potential

Another electrophysiological procedure is relatively free from olfactory interference: the NMP is measured on the level of the nasal mucosa and thus the periphery of the trigeminal system [46.79–83]. The NMP is the summating receptor potentials of chemoreceptors of the trigeminal nerve [46.84] and thus an electrophysiological correlate of trigeminal activation of the nasal respiratory epithelium [46.79–83]. As such it is independent from olfactory stimulation. NMPs are recorded by means of an electrode placed on the respiratory mucosa [46.85]; electrode placement should be done under endoscopical control [46.86]. Again, the signal is averaged, but due to the lower background noise, fewer recordings are needed to obtain a meaningful NMP. In fact, one single recording may be enough for interpretation. Similar to ERP, NMP recording requires an olfactometer for stimulus presentation to assure a sharp stimulus onset and exactly defined duration and to avoid concomitant mechanical and thermal co-stimulation.
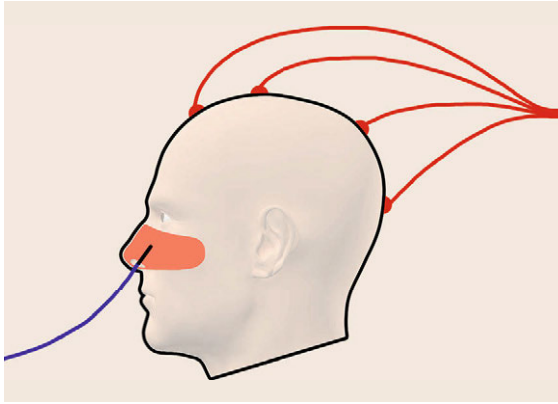
Fig. 46.4 Electrophysiological recording sites: event-related potentials are EEG derived signals and recorded from the surface of the skull (*red*), central responses; negative mucosal potentials are mucosa-generated responses and recorded from the epithelium (*blue*), peripheral responses

NMP consist of a slow negative wave with a latency of approximately 1000 ms [46.87]. The largest NMP indicating the highest sensitivity is observed at the nasal septum, lowest on the nasal floor and the olfactory cleft [46.50, 88]. See Fig. 46.4 for an overview over electrophysiological recording sites.

46.4.3 Brain Imaging

Over the last three decades, several techniques have been made available to neuroscientists, which allow for the investigation of brain structure and brain function in vivo. The most commonly used technique is functional magnetic resonance imaging (MRI), which measures the ratio of oxygenated hemoglobin/deoxygenated hemoglobin in the brain. From this one can infer the activation level of different brain areas (neurovascular coupling). Specifically, researchers can observe which areas of the brain are activated by different tasks. Functional MRI permits the investigation of brain activation with a relatively high spatial resolution. Still, a voxel – the 3D analog of a pixel – typically has the size of $27 \, mm^3$ ($3 \, mm \times 3 \, mm \times 3 \, mm$); thus each voxel contains the information of the average activation of ten thousands of neurons. Functional MRI has been used to explore sensory processing; in some studies the trigeminal system has been examined with this technique. Functional MRI has shown that chemosensory trigeminal stimulation leads to the activation patterns which only partly overlap with somatosensory stimuli (brainstem [46.14], thalamus [46.13], SI/SII [46.89], anterior cingulate [46.14]). However, chemosensory trigeminal stimuli also activate olfactory regions, piriform, orbitofrontal, and insular cortex [46.12, 14, 90]. It is worth mentioning that especially orbitofrontal areas are susceptible to image distortion in MRI due to the proximity of the nasal sinuses making the examination of this chemosensory area somewhat difficult.

Other brain imaging techniques can be used to investigate the trigeminal system, but have so far only been used in a few studies. One of these techniques, PET assesses the concentration of radioactive markers. Importantly, it allows for imaging of the orbitofrontal areas of the brain free of distortion; however, this comes with a weaker spatial and temporal resolution compared to functional MRI. PET-based experiments reported additional activation in the amygdala, claustrum, and lateral hypothalamus due to trigeminal chemosensory stimulation [46.91].

46.5 Interactions Between Olfaction and Trigeminal System

As mentioned earlier, most stimuli activate the trigeminal system as well as the olfactory system [46.51, 92, 93]. Additionally, psychophysical and electrophysiological findings report that these two systems interact [46.93], by suppression and enhancing each other [46.92, 94–98]. It is hypothesized that this interaction occurs at three levels:

1. On the stimulus level
2. In the periphery (mucosa)
3. On central levels (brain; Fig. 46.5) [46.92].

In order to understand this interaction, it is necessary to evaluate both sensory systems separately. However the fact that they are usually stimulated together raises a serious methodological challenge. One possibility to overcome this problem is to investigate the trigeminal function in subjects without a working sense of smell [46.93].

46.5.1 Stimuli

Subjects with anosmia are able to detect a large number of volatile chemicals despite the lack of functionality of the olfactory nerve, suggesting that stimuli perception was processed by the trigeminal nerve [46.15]. Moreover, patients with olfactory dysfunction also demonstrate lower trigeminal sensitivity which highlights the interdependence of the two systems [46.99, 100]. Additionally, healthy subjects have higher trigeminal thresholds compared to olfactory ones suggesting
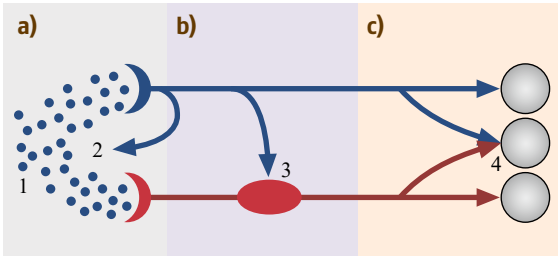
Fig. 46.5 Sites of interaction between the trigeminal system (*blue*) and the olfactory system (*red*). (a) Mucosal level: 1. The same molecules can stimulate both, the olfactory system and the trigeminal system; 2. Trigeminal reflexes may alter nasal patency. (b) Olfactory bulb: 3. Some trigeminal nerve endings terminate in the olfactory bulb. (c) Central nervous system: 4. The trigeminal system and the olfactory system share central processing units

that it takes a higher concentration of an odorant to stimulate the trigeminal nerve as compare to the olfactory nerve [46.51]. Thus, most odorants also activate the trigeminal system. It should be noted however that although most odorants activate both, the trigeminal and the olfactory nerves, there are a few exceptions. For instance, CO_2 activates the trigeminal system with little or no concomitant olfactory stimulation [46.101–103]. On the other hand only a few odorants activate the olfactory nerve selectively with little activation of the trigeminal nerve [46.15] such as vanillin [46.104] decanoic acid [46.15], hydrogen sulfide (H_2S) [46.104] and phenylethyl alcohol (PEA) [46.51, 63].

Further, most irritants that stimulate the trigeminal system can activate the olfactory system as well. This has been shown indirectly, as trigeminal stimulation activates regions typically involved in the olfactory processing such as piriform cortex [46.12, 105], the anterior orbitofrontal cortex [46.12, 106–108], rostral insula [46.12, 109], and the superior temporal gyrus [46.12, 110]. In addition, CO_2, which is usually considered to be a selective trigeminal stimulus, recruited the olfactory pathways in low concentrations [46.111]. Moreover, roughly 10% of piriform cortex neurons responded to both, olfactory and trigeminal stimuli, further highlighting the overlap between the two systems. Altogether, these studies show that both sensory systems exhibit a large extent of promiscuity already on the level of the stimuli.

46.5.2 Indirect Interaction

On top of an interaction at the level of the stimuli, there is also an indirect interaction between the trigeminal and the olfactory systems. For instance, trigeminal reflexes trigger alteration of nasal patency and respiration

as well as changes in the mucus covering the epithelium as a result of the stimulation of glands and secretory cells [46.112]. Additionally, electrophysiological studies indicate that odors can modify, via local axon reflex, the spontaneous activity of olfactory receptor cells which triggers the release of different peptides as well as analgesic effects from trigeminal fibers innervating the olfactory epithelium resulting in a modification of odor perception [46.113–115]. Putting together, these studies indicate that other substances can influence the olfactory and the trigeminal systems [46.93].

46.5.3 Peripheral Interaction

In addition to a complete loss of olfaction, subjects with anosmia also have a lower trigeminal function, when assessed with behavioral measures [46.93, 100, 103, 116, 117]. On peripheral levels however, subjects with anosmia exhibit larger NMP, which indicated increased peripheral susceptibility [46.68, 87]. Thus, a model with mixed sensory adaptation/compensation was put forward to explain the interaction between the two systems at a peripheral level. Some neuroanatomical studies provide underpinnings for these interactions. For example, axons of the trigeminal nerve re-enter the central nervous system (CNS) and terminate in the glomerular layer of the olfactory bulb [46.16, 118]. They may be activated by the lateral excitatory network within the olfactory glomeruli [46.119] of a working olfactory system, which is associated with a reduced peripheral responsiveness [46.74]. In the case of olfactory loss, however, this excitatory network is no longer activated; as a consequence, the intrabulbar trigeminal collaterals become disinhibited, resulting in an increased activation of the trigeminal system at peripheral levels [46.93]. In other words, the lack of a functioning olfactory system leads to the disinhibition of the intrabulbar trigeminal collaterals which results in higher NMP activations. This type of mechanism is also found in the gustatory system in which input from the chorda tympani inhibits that of the glossopharyngeal nerve. Damage to the chorda tympani abolishes this inhibition which increases the input from areas innervated by the glossopharyngeal nerve [46.120].

46.5.4 Central Interaction

Studies on patients with anosmia also revealed interactions of the two systems at central levels. When evaluating such interaction at central levels, electrophysiological measures are particularly useful. Trigeminal event-related potentials (tERPs) are electrophysiological responses generated by the cortex. Compared to controls, subjects with acquired anos-

mia exhibited smaller tERPs [46.87], whereas those with congenital anosmia presented similar activations as controls [46.68]. Moreover, low concentrations of isopentyl acetate (an odor with trigeminal components), triggered odor-like responses in the piriform cortex of mice whereas at high concentrations triggered trigeminal-like responses providing support that some neurons of the piriform cortex can be modulated to respond to both types of stimuli [46.121]. Additionally, the duration of olfactory dysfunction and tERP amplitudes are positively correlated [46.59] suggesting that anosmia-triggered reduction of trigeminal sensitivity could improve over time. Therefore, these studies advocate that on one hand, a fully functional trigeminal system relies on the functionality of the olfactory system [46.58–60, 68, 122, 123], and on the other hand, longer the period of time of olfactory loss, better the adaptive mechanisms. FMRI studies provide further evidence as to the key areas of central interaction between olfactory and trigeminal stimulation [46.12, 90]. While each sensory system has unique central processing areas, they share a considerable amount of central processing areas. For example, activation of brainstem, ventrolateral posterior thalamus, anterior cingulate, precentral gyrus, and somatosensory areas are commonly observed following trigeminal stimulation, but not after exposure to odors [46.14]. In turn, activation of amygdala and the ventral putamen is a typical feature of olfactory but not of nonpainful trigeminal stimulation [46.124]. However, both trigeminal and olfactory stimulation activate piriform cortex, the orbitofrontal cortex and the rostral insula [46.14, 124]. Thus, these are the prime candidates on the quest for the areas of interaction between the trigeminal and the olfactory system. In fact, patients with anosmia exhibited, when compared to controls, less activations in, amongst other regions, the orbitofrontal cortex and the insula, but also primary somatosensory cortex [46.89]. This may help explaining smaller tERP amplitudes and higher trigeminal thresholds in this patient group [46.93]. In healthy subjects a mixture of CO_2 (trigeminal stimuli) and PEA (pure odorant) led to higher activations than the sum of activation of CO_2 and PEA presented independently, in both, chemosensory areas (orbitofrontal cortex) and multisensory integration centers (intraparietal sulcus) [46.125].

Putting together, these imaging studies suggest a great overlap between the two chemical senses highlighting the intimate connections between the two systems.

46.6 Clinical Aspects of the Trigeminal System

Different factors may affect trigeminal sensitivity. The most prominent amongst them is aging as older people consistently exhibit lower trigeminal sensitivity [46.83, 123]. Additionally, different diseases and olfactory dysfunction also impact the trigeminal function [46.59]. As previously mentioned, the olfactory and trigeminal systems interact with one another at different levels and therefore examining a clinical population with olfactory and trigeminal dysfunction could shed some light on the co-dependence of the two systems.

46.6.1 Olfactory Dysfunction and Trigeminal Perception

Hyposmia (a reduced sense of smell) and anosmia are relatively common in the normal population. It is estimated that around 15% of the population exhibit hyposmia and 5% suffer from anosmia [46.52, 53]. Generally, typical causes of hyposmia and anosmia include sinunasal disease, head trauma, upper respiratory tract infections, or neurodegenerative diseases whereas congenital anosmia occurs only in around 2% of those with anosmia [46.126–128]. Anosmia and hyposmia are associated with lower trigeminal sensitivity when tested with several different techniques. Specifically, subjects with anosmia exhibit less changes in their breathing pattern when inhaling airborne chemicals [46.122, 129], have lower intensity ratings of trigeminal stimuli [46.60], exhibit higher thresholds to irritants [46.58, 130], and have fewer correct answers on lateralization tests [46.62, 123]. Lower trigeminal chemosensitivity seems to be a general feature of acquired anosmia and independent of its etiology [46.123], while congenital anosmia is somewhat different from acquired anosmia. As a matter of fact, congenital anosmia is associated with similar behavioral measures of trigeminal sensitivity as controls [46.68]. Interestingly, somatosensory measures (such as responsiveness to touch) are not affected by olfactory dysfunction [46.57]. Further, peripheral susceptibility seems to be larger in patients with anosmia (congenital or acquired), in sharp contrast to the findings from central and behavioral measures [46.93].

The interactions between anosmia and the trigeminal system seem not be stable over time: the duration of the olfactory loss and the functionality of the trigeminal system are correlated as the latter gets better over time [46.87]. Further, those 10−30% [46.131] of cases

of anosmia which show recovery of olfactory function actually exhibit even larger peripheral responses than those without recovery [46.87] suggesting additional complex mechanisms taking place. Putting together, these studies show that acquired anosmia is associated with lower trigeminal sensitivity, while anosmia in general is associated with increased peripheral responsiveness in the trigeminal system.

46.6.2 Trigeminal Dysfunction and Olfactory Perception

As previously mentioned, the trigeminal nerve is the thickest of the cranial nerve which makes it more resistant to trauma compared to the olfactory nerve [46.87]. Consequently, cases in which the trigeminal nerve is damaged are very scarce. In one experiment, local anaesthesia of the middle nasal meatus resulted in an elevation in detection thresholds of *n*-butanol suggesting that blocking the trigeminal system results in a reduced olfactory function [46.132]. In another report, two subjects with a total unilateral destruction of the trigeminal nerve due to the removal of an acoustic neu-

roma, reported lower odor intensity ratings compared to controls with normal trigeminal function [46.133]. In another case study, a women who, as a result of a meningioma, had a loss of trigeminal function on her left side, exhibited lower olfactory function on the affected side [46.103]. Specifically, NMPs responses, tERPs responses to H_2S (pure odorant) as well as to CO_2 (trigeminal irritant) were reduced on the left side compared to the right side. Additionally, pure odorant detection threshold was 64 times higher on the left side compare to the right side. Putting together, a damaged trigeminal system may have an impact on olfactory perception highlighting once more the interdependence of the two systems at different levels of odor processing.

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