

# **Anosmia: What we know and don't know about it**

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## **Introduction**

There are many cases of smelling disorders, which can impact an individual's ability to smell. In addition, it's important to understand there is a whole population among us who cannot smell (anosmia), who may have grown up never smelling (congenital anosmia), or who have reduced smell (hyposmia). Because the sense of smell is not as severe, life-threatening, or well-known, it is not widely studied. With the lack of research in this field, people with smell disorders have few treatment options. While there is some research on anosmia, the understanding of anosmia has plateaued, with many articles re-visiting known causes and common evaluation methods. More in-depth knowledge, however, is known only to a handful of researchers or specialized doctors. This literature review will discuss the research on anosmia, covering causes and effects of anosmia, with some discussion of physiology. This paper will also analyze relevant research that may point to potential treatments, touching on olfactory dysfunctions that may help us to understand anosmia.

## **Basis of Smell: Pathway and Neurogenesis**

Smell is a special sense because it is processed in a different pathway than other senses. Olfactory information does not go through the thalamus. The neurons also do not follow "labelled lines" that other senses have.<sup>1</sup> These labelled lines refer to neurons specific to each sensation. For the somatosensory neurons, which encode touch sensations, these labelled lines are the reason behind phantom limbs. When a neuron is stimulated, it tells you only pain for what it used to connect to. Instead of labelled lines, the olfactory system uses a "map" of multiple signals that associates each unique combination of signals with a unique odor. Odorants go to the olfactory epithelium, in which there are many olfactory receptor cells, each with a variety of receptor proteins, and with each receptor being specific to one chemical. When you inhale a gas mixture, all the chemical odorants activate a certain set of neurons, all of which simultaneously signal a specific set of glomeruli. The brain reads the glomeruli pattern and recognizes each unique combination as a smell.<sup>1,2</sup>

In addition, the olfactory system is one of the few structures that can perform post-natal neurogenesis, or the creation of new neurons in adult life. Olfactory neurons are continuously regenerated from basal cells in the olfactory tract (OB), every 6 – 8 weeks.<sup>1,3,4</sup> One study showed that killing new neurons resulted in a reduced cell count after 3 weeks, but a control group kept a constant population over time, suggesting there is an associated level of apoptosis to counterbalance the cell growth.

Glia, for instance, contribute to new interneurons in the adult OB, and are essential to neurogenesis.<sup>4,5</sup> Another important aspect of neurogenesis is neuroblast migration. In rodents, the neurons first migrate to the subventricular zone in the brain (SVZ), then join the rostral migratory stream (RMS), which is a stream of cerebral spinal fluid toward the core of the OB.<sup>4,6</sup> Chemicals in each glomerular layer guide migration towards the OB via chemotaxis. However, when there is injury, as one study simulated with lesions, new SVZ neuroblasts migrated towards the injuries rather than the RMS.<sup>4</sup>

Studies also show neural stem cells with potential to produce neurons for the glomeruli and granule cells (part of olfactory pathway) exists in rodent and human OB.<sup>6</sup> Growth factors, synaptic activity, rate of SVZ proliferation all regulate rate of neuronal growth and death in specific areas of the OB and SVZ. These neurons have dopaminergic activity and are controlled by olfactory input.<sup>6</sup> With more input, there's more renewal of olfactory neurons. The renewal of olfactory neurons in adults functions for odor discrimination and plasticity of the olfactory system. The plasticity peaks in early neuronal development, and is progressively lost as cells mature.<sup>6</sup>

## **Causes of Anosmia**

### Genetic

One well known cause of anosmia is Kallmann's Syndrome. It is an x-linked disorder which affects the development and migration of olfactory neurons due to abnormal hormone function.<sup>7</sup> The Kallmann's gene encodes the protein, *anosmin*, guides the migration of GnRH releasing neurons and olfactory nerves towards the hypothalamus. As a result, Kallmann's is characterized by hypogonadism and anosmia.

A lesser known and rarer genetic cause is a homozygous nonsense mutation in the SCN9A gene. This mutation leads to a nonfunctional voltage gated sodium channel, called Nav1.7. The result of this is anosmia or hyposmia associated with pain insensitivity.<sup>8,9</sup> Patients from seven countries with this mutation had similar symptoms. This study suggested the Nav1.7 channel in the olfactory epithelium played a role in olfaction. Another study showed that this channel was expressed in the dorsal root ganglia of the peripheral nervous system instead.<sup>8</sup>

A key part of olfactory detection is having receptors to bind the chemical odorants. Genetic deficits resulting in the lack of olfactory receptors or non-functional odor receptors may lead to specific anosmia.<sup>10</sup> Specific anosmia is a condition where the patient is anosmic towards specific odours only. Single nucleotide polymorphisms<sup>2</sup> in a certain odorant receptor can lead to inability to receive signals towards the specific odorant that receptor should bind to. One study looked at the OR7D4 gene for sensitivity to androstenone. Variants of this gene led to the receptor binding to variants of androstenone.<sup>10</sup> Similar studies suggests this is why odor perception may differ from person to person. One may say sweat is "sweet," but another may perceive it as "pungent."<sup>11</sup>

### Underdeveloped olfactory bulb/tract (physiology)

It has also been suggested that the development of the olfactory centers may be the cause. Something commonly seen in congenitally anosmic patients is the absence or underdevelopment of the OB and olfactory tract.<sup>3,12,13</sup> Because the OB is where the map of the glomeruli lies, decreasing the size of the bulb leads to less specific or lower resolution of odor identification, and absence of it would mean no perception of odors.

The depth of the olfactory sulcus<sup>2,3,12</sup> in the frontal cortex is also reduced for congenital anosmia. A depth of less than or equal to 8mm<sup>13</sup> indicates isolated anosmia, whereas anything deeper does not necessarily suggest anosmia. For healthy individuals, olfactory function is correlated with the volume and thickness of the right frontal cortex where the olfactory sulcus lies. Olfactory function is tied to the left-side cortex, and a thicker piriform cortex (another structure involved in olfaction) was seen in

congenital anosmia.<sup>12</sup> All these structures of the brain play a role in the complex olfactory system. If they are reduced, it may indicate reduced olfactory function.

Amount of neurons may lead to anosmia. Gray matter is composed of cell bodies and synapses and white matter are the axons. White matter is less dense than gray matter, with fewer functionally significant structures, like cell bodies and synapses. MRI Imaging of healthy patients revealed more gray matter correlated with more olfactory function. Congenitally anosmic patients had increased white matter, and those who acquired olfactory dysfunctions had less gray matter.<sup>12</sup> The physiology may lead to anosmia, as it seems there's less neuronal gray matter for anosmics.

#### Trauma (edema/hematoma/epithelium or olfactory bulb)

Post-traumatic olfactory loss is a common form of acquired anosmia. The mechanism behind it may be due to swelling or cutting off of neural pathways, or brain injury redirecting blood flow away from the olfactory system.<sup>14,15</sup> One study showed that post-traumatic olfactory loss improved with edema or hematoma removal. Another study using fMRI imaging found that the trigeminal nerve and the olfactory nerve both have the same blood-dependent brain areas for their responses.<sup>14</sup> Finally, a third study saw reduced cerebral blood flow to olfactory regions of the brain in patients with anosmia.<sup>16</sup> Together, these studies indicate that less blood flow may lead to less olfaction.

Many reported cases reveal that spontaneous recovery occurs around 6 months to a year after the loss of olfaction, although it is unlikely to recover without intervention<sup>15</sup> after this period. This suggests the olfactory epithelium or OB is healing and re-growing tissues and recreating neural connections,<sup>2,17</sup> and is physical damage to the epithelium or OB that reduces olfaction.

There are also many studies that suggest damage resulting in decreased input from olfactory receptor cells can lead to decreased OB volume.<sup>14,15</sup> These studies looked at olfactory loss in post-infectious, post-traumatic, nasal polyposis and sinonasal disease patients.

#### Drug-induced

A less well known cause of anosmia is anosmia due to drugs or medical treatments. Drugs may act as agonists or antagonists,<sup>18</sup> mimicking chemical signals that affect the olfactory pathway. Some drugs may also disturb action potentials. Cells usually use calcium influxes to release signals, but drugs that inhibit these calcium fluxes result in inhibited action potentials<sup>18</sup> between cells. In the same way, certain drugs may alter neurotransmitter signals, inhibiting re-uptake from synaptic cleft leading to over stimulation.<sup>2</sup>

There can be chemical obstructions.<sup>2</sup> A dry mucosa or closed taste pore<sup>18</sup> will prevent odorants from diffusing over to the receptors. The drug itself may create a chemical environment<sup>18</sup> with unfamiliar gradients or unbalanced concentrations of a molecule, adversely influencing signaling or the diffusion of signaling molecules. Infections with inflammations also cause swelling and blockage of odorants towards the receptors. In fact, one study showed rhinosinusitis, which presents with inflammation, often results in a reduced olfactory threshold.<sup>3</sup>

Nicotine<sup>4</sup> could also lead to olfactory disorders. Neurogenesis is vital to the maintenance of olfaction, as explained earlier. One study showed nicotine was detrimental the survival of new cells in the adult OB, and resulted in a reduced cell population, leading to reduced sense of smell.

### Age

Age is known to be associated with hyposmia and anosmia. Data from one study shows the OB volume increased up to 40 years and started to decline afterwards with age.<sup>14</sup> This may be due to the lower amount of available stem cells and decreased turnover rate associated with age. As stated before, olfactory neurons can regenerate, and their performance and plasticity peaks in early neuronal development, and is progressively lost as cells mature.<sup>6</sup> As the neurons grow old, they lose their function. In addition to decreasing neuronal functions, another study suggested there is accelerated apoptosis<sup>3</sup> contributing to turnover rate in older patients.

### Concomitant Diseases

Many diseases and dysfunctions do present with anosmia as a side effect. Internal disorders<sup>3</sup> such as renal failure and diabetes may lead to anosmia. Psychiatric diseases,<sup>3</sup> like schizophrenia and depression can be accompanied by anosmia as well. Neurologic diseases like Alzheimer's and Parkinson's are also known to have olfactory dysfunctions. Anosmia and the characteristic cognitive decline in patients with Alzheimer's and Parkinson's may be due to reduced blood flow to the affected areas, including the olfactory system.<sup>16,19</sup>

One study looked specifically at Parkinson's. This study suggested the cholinergic, serotonergic, noradrenergic systems as well as damage to the dopaminergic system are important to the Parkinson's related olfactory dysfunction.<sup>5</sup> These systems regulate the glial activity which is involved in brain injury processes, and because glia is important for olfactory neurogenesis, damage to these systems could lead to anosmia.

### **Effects of Anosmia**

Anosmia is usually known only by the symptoms, and like any disease or dysfunction, the symptoms are what makes research in the matter crucial and worthy of funding. This sections will discuss how anosmia affects patients and what anosmics experience.

### Olfactory bulb volume

Lack of olfactory stimulation and peripheral sensory input from receptor cells leads to decreased volume of the OB.<sup>13,15</sup> In a study with posttraumatic anosmia, trauma patients with damage affecting the pathway from olfactory receptor cells had a decrease in OB volume.

### Intranasal trigeminal nerve

Odorants stimulate olfactory receptor neurons as well as the intranasal trigeminal nerve, which provides sensations in the nose like burning, itching or coolness, all of which are separate from the olfactory system.<sup>14,20</sup> These are touch sensations that can contribute to the perception of an odor. Specifically, they are pain sensations, due to the presence of chemosensitive nociceptors and pain fibers. Anosmic patients were less sensitive to trigeminal sensations, meaning there was a higher threshold for stimulation of the nerve.<sup>20</sup> When presented with stimuli, anosmics has smaller amplitudes recorded from the trigeminal nerve. However, with a longitudinal study, it was found that with time, trigeminal sensitivity recovered. Patients scored higher in later olfaction tests compared to testing soon after the loss of olfaction. Anosmic patients also have larger responses reflecting trigeminal activation in

the respiratory epithelium. One study observed that anosmics had higher peripheral responses to CO<sub>2</sub> presentation, meaning their autonomic nervous system was more responsive than in healthy persons.

### Emotional/psychological

Olfactory loss can impact the quality of life, often resulting from the loss of flavor of foods, as aromas are no longer present to accompany the taste. Patients with olfactory loss report bland tasting foods and cooking without smelling aromas, leading to weight loss and depression.<sup>3</sup>

Also, with the absence of sense of smell, anosmic patients also need to monitor facial expressions from others to gauge hazards. In one study, longer term anosmia led to more accurate fear and disgust recognition because of their decreased ability to detect environmental hazards.<sup>21</sup>

### Smell and Taste

Although it is commonly believed taste and smell go hand in hand, they are independent. The perception of taste is called flavor, which results from unique associations of three different systems. The gustatory system senses five basic tastes: sweet, sour, salty, bitter, and umami. The olfactory nerve senses a range of gaseous odorants, like vanilla or rotten eggs. The trigeminal nerve senses touch sensations, like the tingling or stinging of vapors. The combination of these contribute to the perception of taste.<sup>22</sup> Although loss of smell may dull flavor, it does not follow that congenital anosmics lack taste.

## **Research on Olfactory Disorders and Prospective treatments**

### Parosmia

Some interesting research on parosmia, the distorted identification of odors, may shed light into the mechanism of olfactory receptor neuron growth. Earlier, the physiology of the olfactory system was discussed, going over the “map” of signals that creates what we perceive as smell. In parosmia, the olfactory neurons are still present, but some are lost or damaged.<sup>17</sup> The patient can still perceive odors, but with certain neurons missing, the map created by a gaseous mixture is incomplete, and the “smell” would be skewed. Parosmia can also result from problems with the integrative centers of the central nervous system, where olfactory information is misinterpreted. It is suggested that following damage, the regenerating olfactory epithelium and OB get rewired incorrectly.<sup>17</sup> This means, that as the neurons grow back and try to reform the original synapses, they may actually connect with the wrong or different neurons and signal different cells leading to different “maps” created when sent to the glomeruli. A significant number of parosmias occur after upper respiratory tract infections (URTIs) or trauma, and then are followed by anosmia or hyposmia. Parosmias are more closely associated with hyposmia, indicating that the olfactory function is still intact at the olfactory epithelium and OB.<sup>17</sup>

### Steroids

Systemic and topical steroid are commonly used to treat anosmia, although there are no clear results. Systemically used steroid are injected or taken orally. Topically used steroid are applied like a lotion to a specific area.

Systemic steroids and oral steroids have been shown to improve olfaction, but the mechanism behind this remains unknown.<sup>3,15</sup> Studies showed rapid improvement if doses were administered

constantly after surgery. However, topical steroid sprays showed no significant improvement. One study in Japan showed improvement with long-term administration of low-dose macrolides.<sup>3</sup>

Another study looked at the threshold, discrimination and identification (TDI) score to measure improvement with steroid therapy. Topical steroids had a significant benefit in non-steroid-responsive anosmia, especially when budesonid was applied with neomycin.<sup>23</sup> For steroid sensitive and non-steroid sensitive anosmia, initial systemic steroids also showed some improvement.

#### Zinc treatment

Oral steroid treatments like Prednisolone has had mixed results as therapy, while other drugs like minocycline, Vitamin A, or herbal drug combinations were not successful.<sup>24</sup> One study focused on prednisolone in combination with zinc gluconate. The study administered the zinc for a month, with high-doses of prednisolone initially, and tapering off for 2 weeks. This resulted in improvement for 28% of patients. In comparison, 25% improved with just zinc, and 11% improved with only prednisolone, and spontaneous recovery rate with no treatment was 2%. The study also noted the OB did not change for those who improved. The study suggested that zinc would be helpful in treating patients with loss of smell, as Zinc<sup>25</sup> seemed to be involved with regenerating olfactory neurons. Younger patients had stronger improvement, indicating age may be a factor in neuronal regeneration.

#### Olfactory training

One study looked at long term training, over 32 weeks. Patients exposed themselves twice daily to four odors for roughly 10 seconds. Olfaction did increase. However, this training was done with patients who lost their sense of smell under 24 months after a URTI. Previous studies have suggested that repeated exposure to odors can stimulate olfactory neuron growth, as well as increase the expression of olfactory receptors in these neurons. Even so, these studies only looked at olfactory loss following URTI, trauma, Parkinson's disease, or idiopathic etiology. The success of olfactory training may be due to olfactory neurons<sup>3</sup> still being present. For congenital anosmia and anosmia resulting from genetic deficits, the receptors or neurons are not present and cannot be created or bypassed with olfactory training. Also, it is important to note training improved odor discrimination, not the threshold for odor perception.<sup>24</sup>

#### Surgical interventions

Surgery has been used to remove drainage allowed healing of inflammations, which restored signal conduction pathways.<sup>3,15</sup> It is the most common treatment for post-traumatic anosmia or URTI. Surgery to remove obstructions is currently the only treatment known to physicians who are not specialized in olfaction.

#### **Conclusion: Future Steps**

This review has discussed the olfactory pathway for smell perception and neurogenesis in the olfactory bulb. Genetic, physical, chemical causes, as well as agenesis or concomitant disease are all valid causes of anosmia. Anosmia leads to a decreased olfactory bulb and emotional effects, with remaining trigeminal and taste sensations. Research on parosmia mechanisms can shed light on how anosmia may develop. Finally, results from zinc treatments, steroid therapy, or olfactory training are not definitive, and surgery is currently the most successful for trauma and URTI patients. There is not

enough research to show that any one treatment is significantly successful. A better understanding of the chemical mechanisms, signaling pathways and odor recognition is needed. Although people with olfactory dysfunctions such as anosmia can find a way to live with their condition, there is much interest in anosmia treatments amongst the anosmic community.

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