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Understanding changes in the olfactory system could help with early diagnosis and treatment of Anosmia

Abstract:
Introduction. Anosmia is an olfactory disease that is associated with the inability to smell. This disease affects 3-20% of the population, consisting of younger as well as aged adults. Anosmia is found mostly in aged adults, that are 40 years and older, and is prevalent in men. This disease can occur due to various reasons, such as sinonasal diseases, traumatic head injury, neurodegenerative diseases, viral infections, and upper respiratory infections. Anosmia can reduce quality of life, as they tend to miss out on many warning odors from food or the environment, as well as social experiences, and the overall feeling of well-being [1]. Being able to properly diagnose and treat this condition in a timely fashion is extremely important, as it could potentially recover subjects' sense of smell and taste. This condition has been prevalent in recent months due to the SARS-Cov-2 pandemic, in which many people reported having a loss of smell and taste, however, it was also found that this is not a direct result of the SARS-Cov-2 coronavirus, as the neurons themselves were untouched by the virus, but the sustentacular and olfactory stem cells, which support the neurons, were damaged, causing the neurons to be exposed and harmed, indirectly causing anosmia [2].

Methods/Results. This condition is usually tested using electroencephalography (EEG) to detect whether brain signals occur when participants are presented with odors, but with the low signal-to-noise ratio, it is difficult to understand differences in brain activity between subjects with anosmia as well as those that do not have this condition. A newer approach that has been used to amplify and/or improve the signal-to-noise ratio is using controlled entropy evaluation of the EEG signals that align with the time at which the odorant was presented to the subjects [3]. This diagnostic tool gave a diagnostic accuracy of over 75%, showing that this could be a very promising tool to correctly diagnose anosmia. Neuroplasticity generally occurs with traumatic injuries, so to further understand these effects, functional magnetic resonance imaging (fMRI) was used in a particular study [4]. This method showed that there were less intra-network connections within the brain, with more inter-network connections. Thus, using fMRI allows us to see how neuroplasticity could possibly induce anosmia in patients with traumatic injuries.

Conclusion. Overall, anosmia is a condition in which one cannot smell, and in turn, cannot taste, leaving adults with a lower quality of life. Understanding diagnosis through the use of different methods such as fMRI or through analyzing EEG signals can guide us toward better treatments as well as early detection.

Introduction

Anosmia is a disease of the olfactory neuronal cells that are located in the nose. This condition results in a loss of the sense of smell, and results in an overall low quality of life. Anosmia may also harm those suffering with this condition as they would be unable to detect warning odors or eat spoiled food. Smells are directly linked to emotions, so it has also been found that most anosmics are depressed. Research has shown that this condition is most prevalent in men of older age, however it is still common in male and females of a young age as

well. Anosmia can be caused due to a variety of reasons. The most common causes are due to complications with traumatic head and nose injuries or severe rhinitis or sinusoidal infections [1]. This can also cause neuroplasticity, resulting in cell functions different from normal functions [4].

Kang et. al analyzed data gathered with the Korean National Health Insurance Service about anosmia from 2006 to 2016. From this data, they found the prevalence and incidence of the condition within the different age groups as well as throughout the years. They found that in 2015, there was a higher prevalence of anosmia within the age group of 30-49 years old compared to the other groups (**FIG 1**). Although this finding is common among other studies as well, one factor that was found in Kang et al.'s study is that the data may be skewed due to the incidence and prevalence rates coming only from those patients that had gone to the hospital themselves to check their conditions [5]. Thus, it may be important to test this finding among other studies, especially those in which the patients have not self-reported the condition.

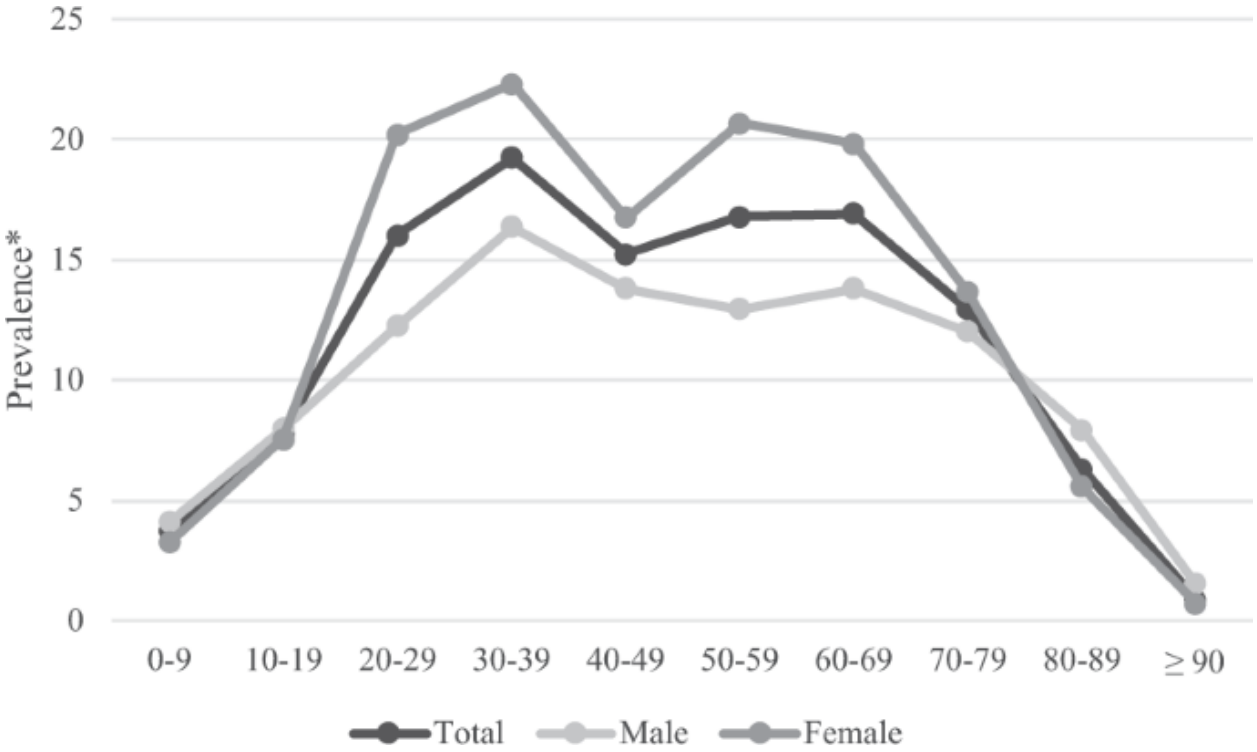
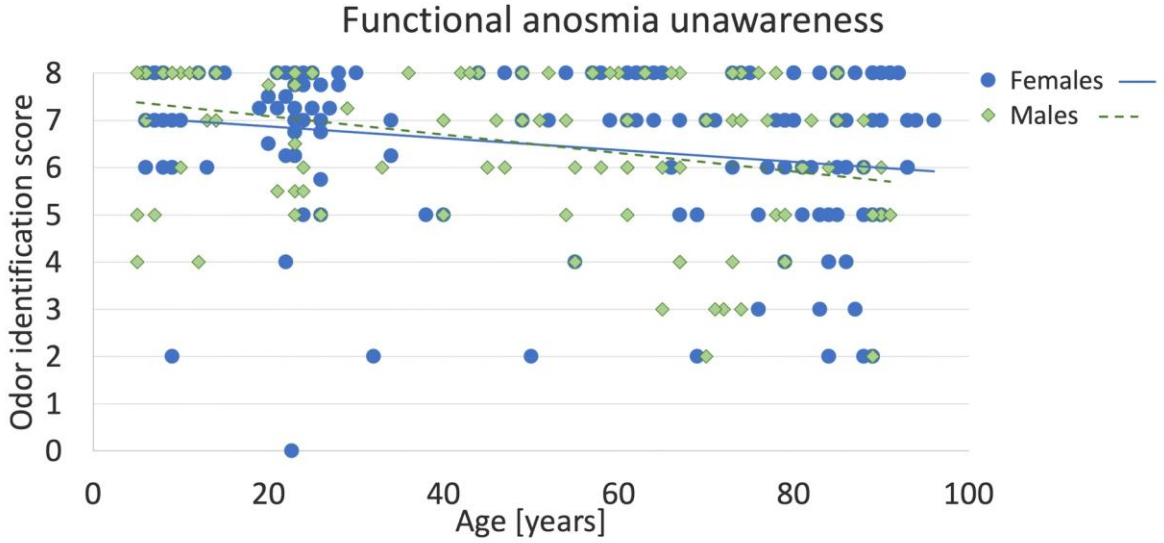


FIG 1. This image shows the prevalence of anosmia in males and females of the age groups shown on the x-axis below, in the year 2015. There is also a solid black line that shows the median prevalence between the males and females of each age group [5].

This factor was accounted in the study by A. Oleszkiewicz and T. Hummel when they found functional anosmia in individuals that were unaware of their condition. Although it was found that in each age group, it was a very small percentage found, excluding the 80+ age group in which 58% were found to be anosmic, it is still worth noting that anosmia can come in this different form, in which the individuals do not feel any olfactory impairment, but can still be diagnosed as anosmic. Those that are experiencing this peculiar phenomenon usually can smell, but they cannot identify the odor correctly. In other words, they have not lost their sense of smell, but their sense of odor identification is not accurate (**FIG 2**). This study further shows

that there is a high need for accurate and early detection of anosmia, as well as the availability of proper screening tools [6].



Age [years]	5-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	80+
Number of functionally anosmic individuals	45	19	48	10	15	20	32	38	83
% of to age category	7%	1.4%	1.7%	0.9%	1.8%	2.7%	6.9%	18%	58%

FIG 2. This image shows the prevalence of functional anosmia in those people that have declared no olfactory impairment. From this, it can be seen that each age group has functionally anosmic individuals that did not know they had this condition [6].

Importance of Early Detection

As in any disease, early detection allows for prompt response and more effective treatment for patients. In anosmia, it is important to understand the cause as well as the threshold of anosmia for each patient. Most patients become anosmic due to traumatic injuries to the head or nose, or severe infections in the nose, such as rhinitis, or sinusoidal infections. However, due to the severity of the injury or infection, the patients may have some sense of smell or none at all. Rouby et. al conducted a validation study on a test called the Lyon Clinical Olfactory Test (LCOT) to understand the threshold for patients with and without anosmia. They accounted for male patients that were of an older age, as that is the age group in which anosmia is highly prevalent. This group used blocks with four different vials in each, with one having an odorant, while the other three were blank, to test the threshold of each patient, and to see whether the patient was truly anosmic or was hyposmic, which is anosmia at a very low severity, allowing them to smell more than those with anosmia [8]. Overall, the test proved to be useful as they were able to correctly identify the patients that were anosmic with the questionnaires and supporting information found from the LCOT.

Research has shown that detecting anosmia is not a straightforward process. Temmel et. al reported that there are many factors involved in diagnosing anosmia, such as gender, age, predisposition to injuries or other diseases. Of the 278 participants in the study, 4% of the patients that had reported normal olfactory function were found to be either hyposmic or anosmic. These 4% that had self-misdiagnosed themselves had reported several occasions

where their quality of life had decreased, but they were unsure of the cause until they participated in this study. This study also provided evidence that a longer duration of olfactory loss could hurt the chances of recovery from the condition [8]. Although there is no cure, recovery does occur for anosmics, but the recovery process and the extent of the recovery depends on the cause and the extent of the anosmic condition. Therefore, this study gave further indication of the importance of early and accurate detection of anosmia.

Anosmia with SARS-Cov-2

The SARS-Cov-2 virus has resulted in many unknown and unusual symptoms. One of those unusual symptoms is the loss of smell and taste. Many believe that the olfactory sensor neurons that are responsible for the sense of smell that are found in the nose have been affected, causing this unique symptom. Upon further research, it was found that the actual neurons were not destroyed or harmed by the virus, but the cells that were surrounding it had been destroyed. SARS-Cov-2 has a spike protein on its surface which attaches to the angiotensin-converting enzyme (ACE2), and is further cleaved by the TMPRSS2 gene, releasing the virus inside the body. It was found that these two key entry genes were found in high levels in the mucosal lining of the nasal cavity [2]. Interestingly, the olfactory sensory neurons do not produce these genes, so they were not the source of entry for the virus, and therefore cannot be directly affected by it. However, the cells that are part of the mucosal lining that covers and protects these olfactory sensory neurons are compromised. These cells are the olfactory stem cells and sustentacular cells that protect the neurons. This leaves the neurons exposed, and prone to harm from other impurities, causing those affected by the virus to have a loss of the sense of smell and taste. Eventually, the mucosal lining is built up again, and the olfactory sensory neurons have a stable environment in which they can function properly again. Another indicator is that recovery of anosmia in these people usually lasts a few weeks, while with other cases in which anosmia was found, especially in those with sinonasal diseases, the recovery usually lasts a few months.

Methods of Detection

The most common and widely used method of detecting anosmia is using the Sniffin' Sticks test, which consists of sticks that are soaked with specific odors, allowing individuals to identify the odor based on the saturated scent on the sticks (**FIG 3**). As the name suggests, one scratches the stick and then sniffs the stick to identify the odor based on what he or she smells [6]. When this method was used in the study conducted in South Korea, it was found that the participants that did not have anosmia were also not familiar with more than half of the odors on the original sniffing sticks, so they had adapted this method to include more smells that are characteristic of South Korea, so the test could be more useful in the comparison between participants with and without anosmia [5]. This method is commonly used as they are very easy to obtain and create as well as adapt for different countries and cultures.

FIG 3. The Sniffin' Sticks test is shown here where the blindfolded participant is smelling the stick in order to identify the smell on the stick [7].

Another method of detecting anosmia is using the Lyon Clinical Olfactory Test (LCOT). In this method, the individual is given four vials of size 15 mL, in which only one vial contains an odorant dissolved in oil, while the remaining three only have oil in it. This method can then be repeated with different thresholds or concentrations of the odorant in the one vial. In other words, the individual will then be asked to identify the vial with the odor at different concentrations in order to identify the odor correctly. This method was tested and validated using two common odors, mint and gas, by Rouby et al. In their sample, they accounted for the older aged population, and were also very representative of the population. Although the individuals in this study came of their own accord through volunteering, their results showed that the percentages of anosmic, hyposmic, and normal individuals were consistent with results from other studies using the sniffing sticks method [8]. This further validates this method as a good and accurate method of characterizing anosmia.

Another interesting method of detecting anosmia is using entropy evaluation from EEG signals. EEG is not a typical way of detecting anosmia due to the low signal to noise ratio as well as environmental factors. Entropy is a measure of complexity of the signal that results from an internal or external event. Since the EEG signals start to change its complexity and entropy is increased when this event occurs, Güdücü et al. took this idea and measured entropy when the individuals were asked to smell something. This method relies on the idea that a change in entropy during the smelling event is characteristic of the object being smelled, compared to no change in entropy in anosmic individuals, where they cannot smell. This method was found to be a better way to detect than just trying to use EEG signals, as this method allowed the signals that relate to the odor to be filtered well and identified more easily [3].

Another way to achieve a baseline detection for anosmia is using functional magnetic resonance imaging (fMRI) of the brain during olfactory activation through an external smelling event. Wang et al. tested and validated this method, providing the baseline for detection, as the differences between the brain fMRI images of younger adults as well as older adults showed

that there was more activity during olfactory activation in younger adults, while older adults had some activity, but it was localized into specific places and was at a smaller scale than in younger adults. The fMRI images that were obtained in this study were filtered so that the signals and activity that was shown was specific to the olfactory activation, so that the activity could be accurately studied [4]. Overall, this method was found to be a good method, but it could prove to be an expensive and inaccessible method to detect compared to the previously mentioned methods. However, this method would allow medical professionals to detect anosmia, by using the baseline detections for normal individuals from this study to compare to those that are believed to have anosmia.

Treatments for Anosmia

Although there is no cure for anosmia, many treatments for this condition exist, but results from the different treatments may vary. This variability is due to the cause of anosmia. Usually, if the anosmia is a leftover symptom of a sinonasal disease, the anosmia can be corrected or retrieved through medicine, topical creams or oils, or surgical practices that would drain the fluid from the nose, allowing air to freely move through the nasal cavity. These treatments can sometimes be used when the anosmia results from nasal obstruction. In these cases, rhinoplasty can also be used to treat the condition. Lifestyle changes can also be another treatment method, such as cessation of smoking if that could be causing anosmia, or if one is unhealthy, having better health choices in terms of food and exercise could help relieve anosmia. However, if the anosmia is caused from something that is not either of these, trying any of these treatments may not help the anosmia be corrected [9]. All of these can be used to try and treat anosmia, but this shows that it is very important to determine the cause of anosmia before choosing the best and effective treatment in each case.

Another promising treatment is using the corticosteroid prednisolone with olfactory training. In this treatment, taking prednisolone was paired with training the nose with various smells in order to regain the sense of smell. The participants were asked to smell the same odors over and over, whilst taking prednisolone. By the end of the course of treatment, over 50% of the participants had regained their sense of smell. One drawback of this could be that the participants were given the same odor repeatedly, which could lead to some participants identifying it from memory rather than the actual odor. Nevertheless, this method proved to help treat more than half of the participants, so it is definitely worthy of further research.

Conclusion

Overall, anosmia is a very wide and very common condition. Although causes of anosmia are varied and it is hard to determine the definitive cause of the condition, early and accurate detection is very important in order to effectively treat the condition. Many methods exist to detect and new methods have been created to make this process more effective. Anosmia is a condition that is in need of more research as it has been prevalent in many diseases, including the SARS-Cov-2 infection that is widespread in today's world. Understanding the differences between normal and anosmic individuals can also help the occurrence of false negatives in anosmic individuals, in other words, those that believed themselves to be normal, but were actually anosmic. All in all, more research is needed on this condition in order to correctly pinpoint the cause of anosmia, so this condition can be effectively

diagnosed, treated, and helped as soon as possible, resulting in a higher quality of life, allowing them to sense warning smells and tastes, as well as regain a healthy mental and emotional state.

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