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# Olfactory Processing and Alzheimer's Disease.

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Running Title: *Olfaction and Alzheimer's*

## Olfactory System.

Living beings are exposed to a constant bombardment of chemical odorant molecules that are detected by specialized structures in the nose called olfactory receptors (9). These olfactory receptors are neurons located in a specialized neuro-epithelium over the back part of the nostrils and there are around a thousand different types that respond to different molecules. These receptors provide the brain with information about a wide range of environmental stimuli ranging from food to sex and the smell system is strongly linked with brain regions controlling both positive and negative emotional responses. Indeed, it is very difficult to perceive an odor without experiencing some concomitant emotional experience, whether pleasure or disgust.

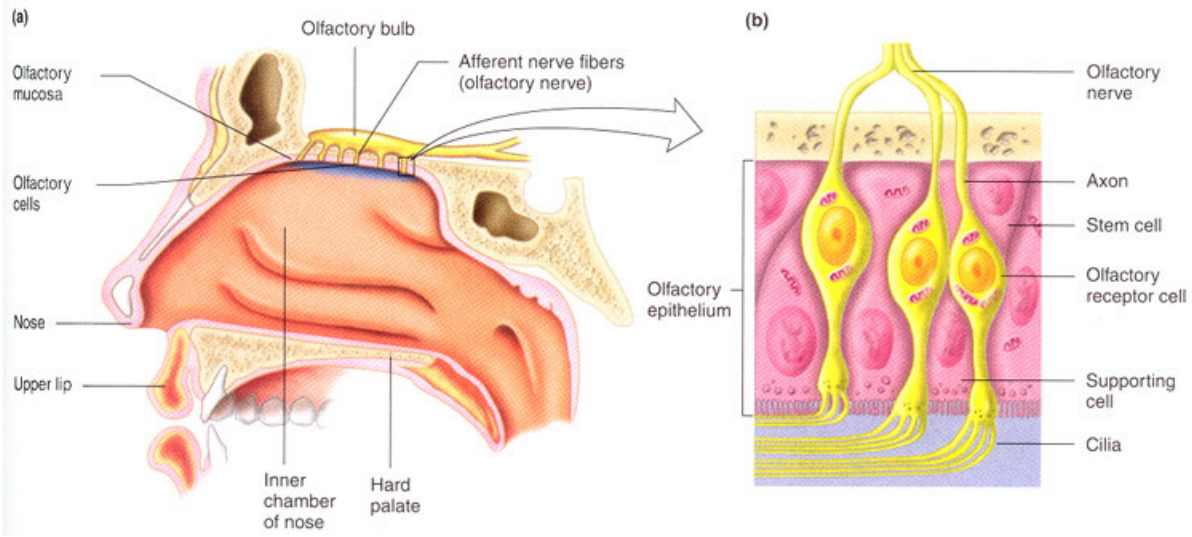


***Figure 1**. (a) Location and (b) enlargement of a portion of the mucosa showing the structure of the olfactory receptor cells.*

The loss of our sense of smell can affect us in terms of not being able to enjoy a good meal or the fragrance of a perfume or a flower. We all know what it is like when we catch a cold and find it difficult to smell or taste anything and this shows that not only is the olfactory sense important for us to be able to smell things but it is also a major contributor to our perception of taste as well. The olfactory receptors and their associated brain processes allow each individual to recognize as many as 10,000 different scents (1). Each one is a bipolar nerve cell and from its apical pole, each one sends a single enlarged

dendrite that extends to the surface of the epithelium **(Figure 1**). Several long non-motile cilia extend out from the tip of the dendrite and along the surface of the olfactory epithelium where they are bathed in mucus (9).

Only one axon rises which goes through the lamina crib of the etmoid bone and reaches the olfactory bulb which is the primary sensory processing region in the brain dealing with odor perception. Under normal circumstances it is likely that a number of different receptors will be activated by the typical complex chemical structures of naturally occurring odors but there are chemical groups that can stimulate a specific receptor. Therefore, the brain must be able to determine the exact combination of activated receptors to be able to distinguish them and to be able to differentiate, for example jasmine from fresh bread odor (22). To do this the brain must be able to compute the different spatial patterns of odorant receptor activation and this means that each activated olfactory neuron has a unique spatial representation (25). So each time our odorant receptors are exposed to a particular odor such as Jasmine the unique pattern of activity that it evokes allows us to identify it quickly and reliably. Similar principles operate in other sensory modalities although only olfaction has such a large number of different types of receptors.

As we age all of our other senses lose some of their acuity and the olfactory sense may be particularly affected since the chemoreceptors are clearly strongly influenced by aging (8). This is why the acuity of the olfactory sense diminishes particularly after the age of 60. Women of all ages are more accurate than men in identifying odors but smoking may damage this ability in both men and women. It is also well known that the olfactory sense is one of the first senses to be affected by dementia (19). Even though we do not yet fully understand how the brain identifies odors it is believed that their chemical composition is of particular importance.

## Olfactory perception research on Alzheimer´s Disease (AD).

Most of the studies on olfactory perception in AD show a reduction or loss of ability to identify recognize and detect scents (7, 16, 17, and 20). This loss is noticeable during the first stages of AD (14,15). Sensitivity loss in terms of detection thresholds can occur but as the cognitive impairment increases there are also problems with odor identification or memory (16,19,21). In our studies we have demonstrated that the familiarity of odors plays an important role in identifying scents. Other elements that may affect odor evaluation are its dispersal vehicle and concentration.

In terms of olfactory identification tests used, the ones most frequently applied to AD patients with different cognitive impairments are the University of Pennsylvania Sensory Identification Test (UPSIT) and the short test to identify odors (B-SIT). However, from the UPSIT data and using control groups (n=63), patients with a slight cognitive impairment (n=147) and patients with AD (n=100), (Tabert et al, 2005) (23), all got a subgroup of 10 scents related to AD risk (for instance, the prediction that a patient with a slight cognitive impairment may go through early and moderate AD). This subgroup of odors was compared with that of the UPSIT and the BSIT in the classification of patients and it strongly predicts the eventual development of AD; the only advantage over the UPSIT is that the BSIT test is more practical as it is shorter.

We have adapted a specific olfactory identification test for use with our Mexican population. We carried out a survey on “Scent familiarity” that involved 1000 Mexicans

around the country with ages ranging from 18 to 94. We found no differences in the familiarity of the odors between the young population (20-27) and the older one (60-94) (**Table I**). When we compared Doty´s odor tests (B-SIT and UPSIT) and Taber´s (10-ITEM) with ours (OFPMEX), selected by our older Mexican population (**Table II**)**,** our results showed clearly that odors like lime, roses, banana, onion, gasoline, chocolate and cinnamon are familiar for American as well as for Mexican populations. We have no doubt that applying our OFPMEX odor test to the older population with a high risk of developing AD it can help detect changes in the olfactory threshold even in patients without cognitive disorder. It therefore it can be considered as a valid diagnostic tool for early AD detection.

## INCIDENCE IN SCENT FAMILIARITY IN BOTH MEXICAN YOUNG AND ADULT POPULATIONS

| | 60-94 AGE RANGE | | 20-27 AGE RANGE | |
|---|---|---|---|---|
| SCENT GROUP | SCENTS AND THEIR RECOGNITION FREQUENCY (%) | | SCENTS AND THEIR RECOGNITION FREQUENCY (%) | |
| CITRICS | ORANGE | 100 | LIME | 100 |
| | LIME | 99.2 | ORANGE | 99.5 |
| | MANDARINE | 98.4 | MANDARINE | 98.4 |
| | GUAYABA | 98.8 | GUAYABA | 96.3 |
| OTHERS | COFFEE | 99.2 | CHILE | 100 |
| | ONION | 98.8 | ONION | 100 |
| | CHILE | 98.8 | COFFEE | 98.4 |
| | CHOCOLATE | 98.1 | CHLORINE | 96.8 |
| | WET SOIL | 97.7 | GASOLINE | 96.3 |
| | COOKED BEAN | 95.7 | COOKED CORN | 95.8 |
| | TOMATO BROTH | 94.6 | | 99.5 |
| AROMATIC HERBS | GARLIC | 99.2 | GARLIC | 98.4 |
| | CINNAMON | 97.7 | CINNAMON | 98.4 |
| FLORAL | CAMOMILE | 97.7 | CAMOMILE | 94.8 |
| | ROSES | 96.5 | ROSES | 98.4 |
| FRUITS | APPLE | 98.8 | APPLE | 97.4 |
| | BANANA | 98.4 | BANANA | 95.3 |
| | PEACH | 97.3 | PEACH | 95.3 |
| | | | PEAR | 95.3 |
| HERBS | CORIANDER | 96.9 | MINT | 96.9 |
| | MINT | 96.5 | CORIANDER | 92.7 |

**Citric, species, floral and herbal scents completely coincide; fruits in 75% and others in 50%, approximately. 16 scents coincide in all.**

***Table I****. Coincidence in scent familiarity in both Mexican young and adult populations.*

**COMPARISON OF SCENTS USED IN THE OLFACTORY RECOGNITION TEST IN US CITIZENS AND FAMILIAR SCENTS PREFERRED BY SENIORS IN THE MEXICAN POPULATION.**

| 10-ITEM | B-SIT | UPSIT | OFPMEX |
|---|---|---|---|
| **Pineapple** | **Pineapple** | **Pineapple** | |
| **Soap** | **Soap** | **Soap** | |
| **Lime** | **Lime** | **Lime** | **Lime** |
| Menthol | Roses | Roses | Roses |
| Clove | Banana | Banana | Banana |
| Skin | Onion | Onion | Onion |
| Strawberry | Gasoline | Gasoline | Gasoline |
| Lillacs | Chocolate | Chocolate | Chocolate |
| Smoke | Cinamon | Cinnamon | Cinnamon |
| Natural Gas | | Peach | Peach |
| | | Orange | Orange |
| | Terpentine | Terpentine | |
| | Thinner | Thinner | |
| | | Car oil, menthol, Regaliz, Ginger cookie, Root beer, wintergreen, watermelon, pine tree, grapefruit, peanut, chewing gum, dill picle, pizza, Cedar tree, coconut, Cheddar cheese, lime, grass, cherry, fruit punch | Mandarin orange, guayaba, coffee, chile, garlic, Coriander, mint, wet soil, cooked bean, tomato broth, chlorine, cooked corn, pear, chamomile, apple |
| **Taber et al, 2005** | **Doty et al, 1996** | **Doty et al, 1984** | **Severiano, Cadena, García and Guevara, 2006** |

***Table II**. Comparison of scents used in the olfactory recognition test in US citizens and familiar scents preferred by seniors in Mexican population.*

## Alzheimer's disease.

Increased human life expectancy has been one of the most outstanding achievements for the social and economic advances achieved in many parts of the modern world. Nevertheless, it does not necessarily follow that health-span is increased in

parallel will lifespan and this means that there are an increasing number of health problems to be tackled in populations who are living longer. Aging is therefore posing a great challenge to health care and particularly due to its impact on increasing the incidence of chronic-degenerative diseases, which represent one of the most important health problems in seniors. AD represents 50-60% of all dementias. Its high increasing index of prevalence sets it as the third or fourth cause of death among seniors (2).

Research on AD is focused mainly on establishing its causes and the mechanisms leading to dementia in order to develop preventive measures that may allow effective treatments to be developed. In this review, we will analyze the general pathology aspects of AD as well as some of the progress being made in its diagnosis.

## Neuropathological Aspects of AD.

The neuropathological characteristics which define AD are: the presence of neuritic plaques, formed by the beta amyloid peptide and neurofibrillary tangles, formed by tau protein. Even though AD mainly shows sporadic forms (90-95%), there are also familial cases related to the presence of presenilin 1 and 2 gene mutations (PS1 and PS2) and the amyloid precursor protein beta (APP-β).

## PS1 and PS2 Gene Mutations.

The PS1 and PS2 genes are located on chromosomes 14 and 1 respectively (6, 12). The presenilins are membrane integrated proteins which need to be synthesized and transported through the endoplasmic reticulum. PS1 as well as PS2 interact with other proteins to form a macromolecular complex that contains γ-secretase activity which is responsible for regulating the intramembrane proteolysis of APP-β (10, 11, 24). The molecular effect of these mutations is the enhancement of γ-secretase activity (5, 26) resulting in overproduction of β-amyloid.

## APP-β Mutations.

APP-β is a membrane glycoprotein that can participate as a growth factor, mediating cell adherence, among other functions. Mutations in the gene of this protein are located near the sites identified by alfa, beta and gamma secretases and increase β-amyloid production. These mutations are found in approximately 1% of all families who develop AD.Gene risk factors associated with the Alzheimer´s Disease.

### a. E4 Apolipoprotein (ApoE4)

In 40 to 65% of the AD patients there is an over expression of ApoE4 (3). Apo/E is a plasma protein with an important role in lipid metabolism and is a cholesterol carrier in body tissues (4; 13). There are three isoforms: ApoE2, ApoE3 and ApoE4 which are located in different aleles (ε2,ε3,ε4) of chromosome 19. ApoE4 is associated with an increased susceptibility to AD development. Neuronal damage can be induced by external agents such as oxidative stress, cytotoxic aminoacid accumulation and β-amyloid

deposits. This damage can be repaired by apolipoproteins, nevertheless as can be seen in **Figure 2**, ApoE4 has a deficient repair mechanism which leads to neuronal damage.

**b. CYP46**

The removal and control of cholesterol homeostasis in the brain (18) is due to conversion of cholesterol to 24S-hidroxicolesterol which is regulated by the cholesterol 24S-hidroxilase (CYP46) enzyme. The brain is the organ with the highest cholesterol content in the human body. It has been previously demonstrated that an excess of cholesterol in hippocampal cells stimulates the rupture of APP-β and, in consequence, β-amyloid peptide accumulation. CYP46 protein alterations, as well as the presence of ApoE4, synergistically increase the development of AD.

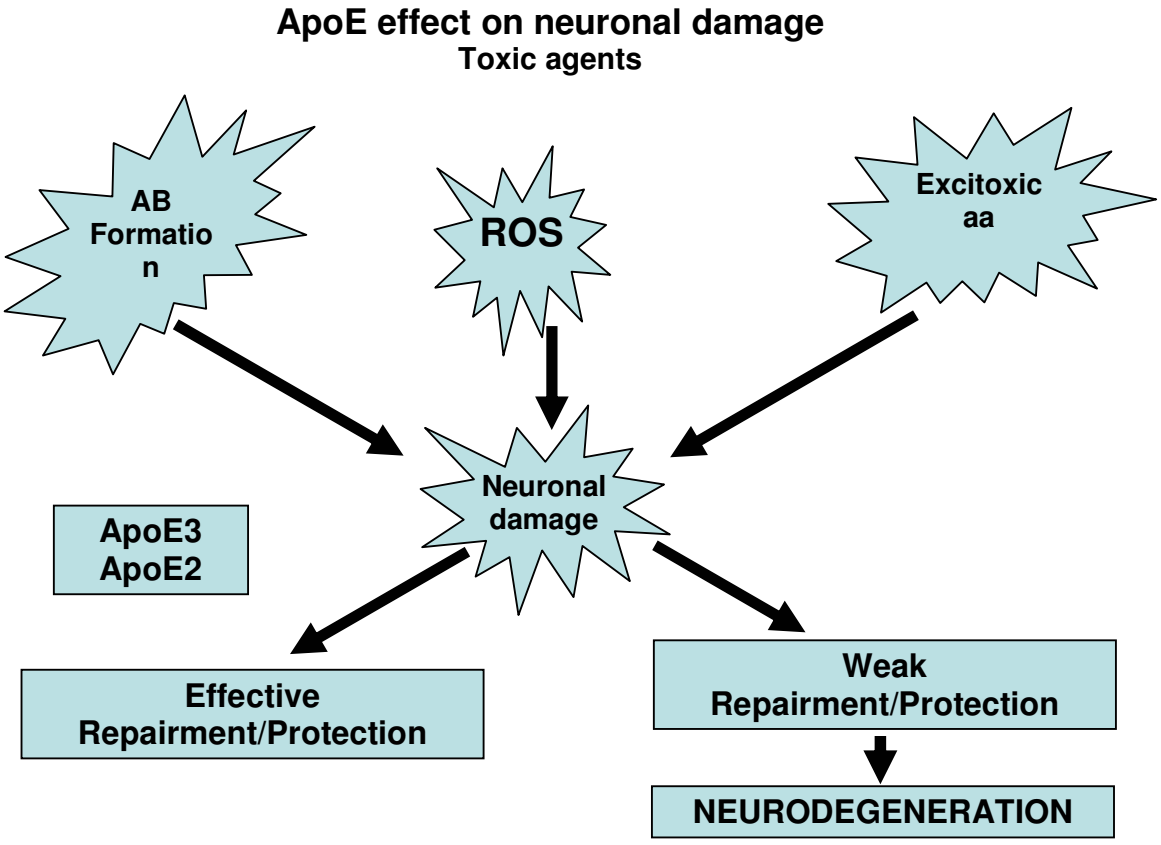


***Figure 2**. Diagram to show the cascade of events responsible of neuronal damage.*

## Conclusions.

Based on our research we are now working on two possible options for early detection of AD. One is based on sensory tests to identify and measure altered olfactory thresholds for specific odors that may be particularly associated with onset of the condition. The second one is based on the quantification of changes molecular markers that may also be linked to degenerative changes in brain structures associated with AD. The advantages of early detection of AD will be that therapeutic intervention can be started

at an earlier stage and hopefully slow the progress of this debilitating disease and help to improve the quality of life for those individuals who develop it.

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