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Neural Basis of Hyposmia in Alzheimer's Disease

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1. Introduction

At the beginning of twenty century Alois Alzheimer described the pathology that now bears his name (Alzheimer, 1907). Over a hundred years later, Alzheimer's disease (AD) is the most common cause of dementia in developed countries. Here eighteen million people are currently affected and the number of patients is expected to increase dramatically with the ongoing increase in the elderly population (Fotuhi et al., 2009, Mount & Downton, 2006). Because no suitable biomarkers are available, the diagnosis of AD remains inconclusive until postmortem pathological analysis, and physicians rely on behavioral manifestations to differentiate between AD and other conditions. For this reason firm diagnosis is generally only made at later stages of the disorder when treatment is purely palliative. These features make AD a social and economic challenge in developed countries (Wimo et al., 2010).

Clinically, AD is characterized by progressive loss of cognitive functions with specific deficits in episodic memory. Clinical diagnosis of is generally only made when cognitive deficits are sufficiently severe to cause dependent status of the patient (Nestor et al., 2004). Pathological analyses of AD brain have described two distinct types of proteinopathy in the frontal and temporal lobes involving the limbic system and the basal forebrain. The first type comprises aggregates of beta-amyloid peptide ($A\beta$) – a specific fragment of the amyloid precursor protein (APP), a plasma membrane protein. These aggregates accumulate in the extracellular space and give rise to senile plaques (SPs). SPs cause synaptotoxicity, neurotoxicity, oxidative stress and hypoxia (Peers et al., 2009, Selkoe, 2001, 2008). The second proteinopathy occurs in the cytosol. Hyperphosphorylation and abnormal aggregation of the microtubule-associated protein tau leads to the intracellular formation of neurofibrillary tangles (NFTs) which cause cytoskeleton destabilization and eventually cell death (Hernandez & Avila, 2008, Selkoe, 2001).

It has been widely reported that olfactory loss (anosmia and hyposmia) takes place in the early stages of AD, and before any detectable cognitive deficits are present. Interestingly, AD pathology extends throughout the limbic system and the basal forebrain, including the olfactory system (Braak & Braak, 1991). The human olfactory system includes peripheral sensory neurons in the olfactory epithelium; these send their axons across the cribriform plate of the etmoides bone to the olfactory bulbs. In the glomerular layer of the olfactory

bulbs their axons synapse with dendrites of the mitral and tufted cells which in turn project to the main olfactory cortex in the basal forebrain. The human olfactory system constitutes complex circuit connections including primary and secondary cortical areas that are connected, as represented schematically in Figure 1.

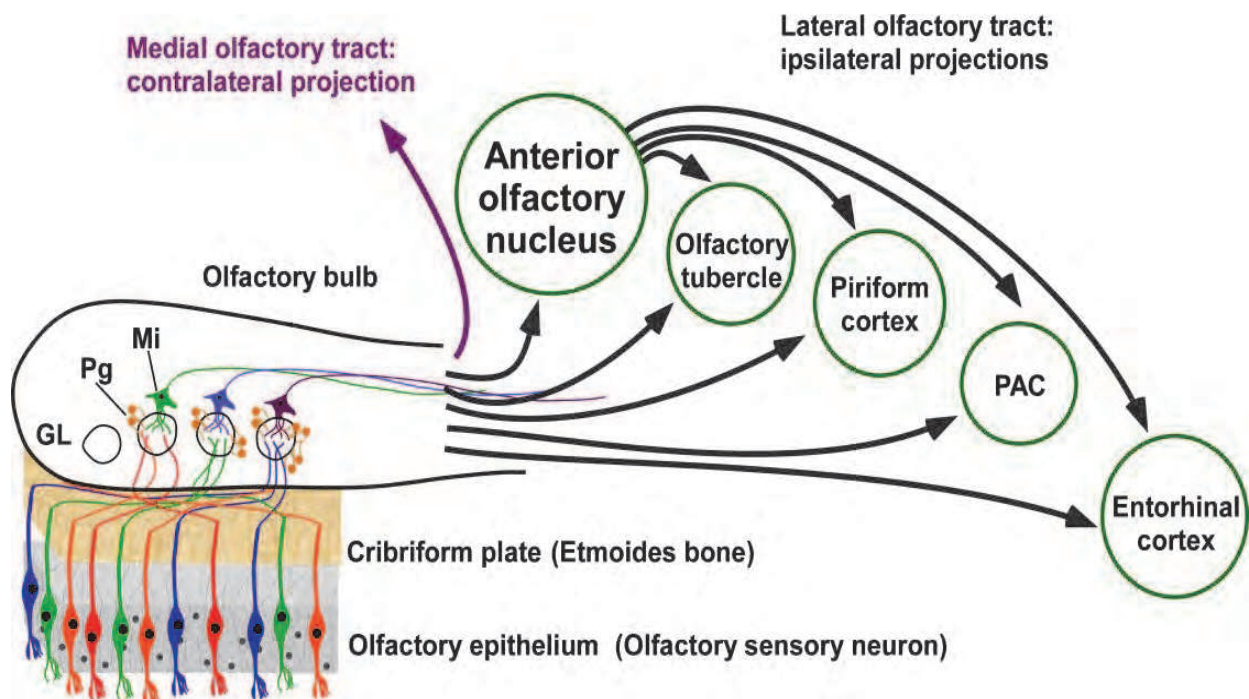


Fig. 1. Schematic diagram of the human olfactory system. GL, glomerular layer; Mi, mitral cell; PAC, periamygdaloid complex; Pg, periglomerular cell.

The progression of AD pathology has been divided into six stages according to the extent of NFT accumulation. Accumulation is first detected in the entorhinal cortex and hippocampus of the limbic system; this extends into the basal forebrain including the olfactory system (Braak & Braak, 1991, Price et al., 1991, Van Hoesen et al., 1991), and from the rostral entorhinal cortex, periamygdaloid cortex, and piriform cortex, to the olfactory tubercle, anterior olfactory nucleus and olfactory bulbs (Fig. 1). Tau pathology has also been described in the olfactory epithelium (Lee et al., 1993). Olfaction is affected in many psychiatric disorders in addition to AD, including Parkinson's disease, Huntington's disease, schizophrenia, senile dementia of Lewy body type, and depression (Atanasova et al., 2008, Kovacs, 2004). It has been widely reported over the past 25 years that olfaction is impaired in AD (Djordjevic et al., 2008, Doty et al., 1987, Meshulam et al., 1998, Murphy, 1999, Murphy et al., 1990, Serby et al., 1985, 1991), and olfaction has become a priority area in the search for biomarkers to establish an early diagnosis of AD and to facilitate early therapeutic intervention (Doty, 2003, Hampel et al., 2010, Hawkes, 2009, Wilson et al., 2009). It has been proposed that the early involvement of the entorhinal cortex and the hippocampus, regions that are tightly related to memory deficiencies (Nagy et al., 1996), could be also the cause of olfactory deficits (Wilson et al., 2007). However, other authors suggest that alternative olfactory areas, for example the posterior part of the piriform cortex, are the specific cause of olfactory deficiencies (Li et al., 2010). Nevertheless, the neural basis underlying hyposmia in the AD brain remain uncertain.

2. Materials and methods

We have studied the olfactory system in 19 AD cases and 7 age-matched controls from the Banc de Teixits Neurològics, Universitat de Barcelona-Hospital Clínic and the Banco de Tejidos/Fundación para Investigaciones Neurológicas, Universidad Complutense de Madrid. Mean ages (\pm standard derivation) in AD and controls were 77.68 ± 9.01 yr and 74.57 ± 4.47 yr, respectively. Tissue samples were fixed by immersion in paraformaldehyde 4% for one month at least. Then, samples were cryoprotected in 30% w/v sucrose and 50 μ m coronal sections were obtained using a sliding freezing microtome.

To study the early stages of disease development we employed a double transgenic mouse model of Alzheimer disease (*App_{swe}/Psen1 Δ 9*). Animals at 2, 4, 6 to 8 months of age ($n = 4$ homozygous and 4 control female mice per group; $N = 32$) were collected for analysis. Animals were anesthetized with a mixture of ketamine hydrochloride (Ketolar, Parke-Davis, Madrid, Spain, 1.5 ml/kg, 75 mg/kg) and xylazine (Xilagesic, Calier, Barcelona, Spain, 0.5 ml/kg, 10 mg/kg). Mice were transcardially perfused with saline solution followed by 4% w/v paraformaldehyde fixative (phosphate buffered; 0.1 M, ph 7.2). Brains were removed from skulls and cryoprotected in 30% w/v sucrose, and sectioned (50 μ m) in the frontal plane (brains) or in the sagittal plane (olfactory bulbs) using a sliding freezing microtome.

In order to delimit areas of interest sections were stained by Nissl technique (Fig. 2A). Primary antibodies used for immunodetection were mouse anti-tau (tau 46, 1:800, Cell Signaling Technology, Beverly, MA, USA), rabbit anti-A β (1:250, Cell Signaling Technology), and goat anti-somatostatin D-20 (1:1000, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Secondary antibodies were either biotinylated (anti-goat IgG, 1:2000, Vector Laboratories, Burlingame, CA, USA) or fluorescent-labeled (1:200, alexas 488 donkey anti-mouse, 568 donkey anti-rabbit, and 350 donkey anti-goat; Molecular Probes, Invitrogen, Carlsbad, CA, USA).

For quantification, somatostatin-positive cells were charted with an X-Y recording system (AccuStage, Minnesota Datametrics, MN, USA). Colocalization levels were measured by confocal microscopy using LSM 710 Zeiss confocal microscope (Carl Zeiss MicroImaging, Barcelona, Spain). Intensities of each fluorochrome were analyzed using the profile tool of the ZEN software (Zeiss).

One-way ANOVA followed by *post hoc* Bonferroni test ($p < 0.05$) was used to estimate significant differences among markers and age groups.

3. Interneurons in the olfactory system

Interneurons constitute 20–30% of the neuronal population of the cerebral cortex and possess distinct morphological, electrophysiological and neurochemical characteristics (Ascoli et al., 2008, DeFelipe, 1997, Markram et al., 2004). Two primary features are common to all interneuron subpopulations. First, these cells are predominantly inhibitory interneurons which express γ -aminobutyric acid (GABA), an inhibitory neurotransmitter; and, second, their neuronal connectivity is predominantly restricted to the local region of the brain (DeFelipe & Farinas, 1992, Kawaguchi & Kondo, 2002).

Interneurons are tightly related to the pathoetiology of AD, and many reports have described the involvement of interneuron subpopulations in AD neuropathology (Attems et al., 2008, Brady & Mufson, 1997, Geula et al., 2003, Saiz-Sanchez et al., 2010, Solodkin et al.,

1996, Supnet & Bezprozvanny). It was recently reported that numbers of interneurons in the entorhinal cortex and hippocampus are significantly reduced in early AD stages (Koliatsos et al., 2006). Interneurons regulate synaptic signaling by pyramidal neurons and the loss of this regulation could produce deficits in learning and memory (Palop et al., 2003, Wallenstein & Hasselmo, 1997). Moreover, dysregulation of olfactory information-processing due to loss of interneurons could underlie the hyposmia described in the early stages of the disease. This review focuses on four major types of interneurons based on their importance to AD etiology and brain calcium homeostasis: respectively cells expressing somatostatin, calbindin, calretinin or parvalbumin. We also discuss the distribution of different types of interneurons and their involvement with tau and β -amyloid pathology as revealed by confocal microscopy.

3.1 Somatostatin

The neuropeptide somatostatin is implicated in diverse functions in the central nervous system (Epelbaum, 1986, Viollet et al., 2008). Somatostatin is expressed in all olfactory areas. Recently, somatostatin has been linked with AD etiology because it is reported to act as a positive regulator of neprilysin, an enzyme which catalyzes the degradation of β -amyloid peptide (Saito et al., 2005). Somatostatin levels decline with aging (Lu et al., 2004) and are further reduced in AD (Davies et al., 1980). It has been proposed that the decline in somatostatin levels with age could explain the age-dependency of AD onset because reduced somatostatin would be expected to lead to downregulation of neprilysin activity, thereby predisposing to the accumulation of β -amyloid peptide (Hama & Saido, 2005).

Confocal microscopy of the olfactory system in AD brain has revealed that somatostatin is selectively reduced, by up to 50%, in olfactory areas such as anterior olfactory nucleus (AON). Moreover, the deficiency in somatostatin was predominantly associated with β -amyloid pathology rather than tau pathology (Figs 2, 3). These findings are in agreement with the theory of Hama & Saido that there is a tight relationship between somatostatin and β -amyloid. The AON is an important relay in olfactory information processing (Price, 1990). Two distinct portions of the AON can be distinguished in the basal forebrain – the medial AON and the lateral AON divided by the olfactory tract (Fig. 2A). The AON is an early site for the accumulation of tau protein (Fig. 2B) (Price et al., 1991) and is also targeted for β -amyloid deposition (Fig. 2C). Somatostatin-expressing cells in the AON possess typical bipolar interneuron morphology. Confocal analyses show that most somatostatin-cells expressing are not associated with tau pathology (Figs 2E, F and 3), and somatostatin-expressing cells are most commonly associated with β -amyloid or with β -amyloid plus tau (Figs 2F and 3).

In *App^{swe}/Psen1 Δ 9* mice, somatostatin is expressed in all olfactory areas. Expression levels decline with age, and are most markedly reduced in the areas where AD initiates, for example the entorhinal cortex. As in the human AD brain, confocal analyses of the olfactory system of double transgenic mice revealed a correlation between somatostatin expression and β -amyloid pathology. Colocalization with β -amyloid peptide was very extensive and was evident in the youngest animals analyzed. Colocalization was seen in all olfactory areas with the exception of the olfactory bulb. Notably, colocalization of somatostatin-expressing interneurons with β -amyloid peptide was evident (Figs 4, 5), even in the absence of reduced levels of somatostatin expression.

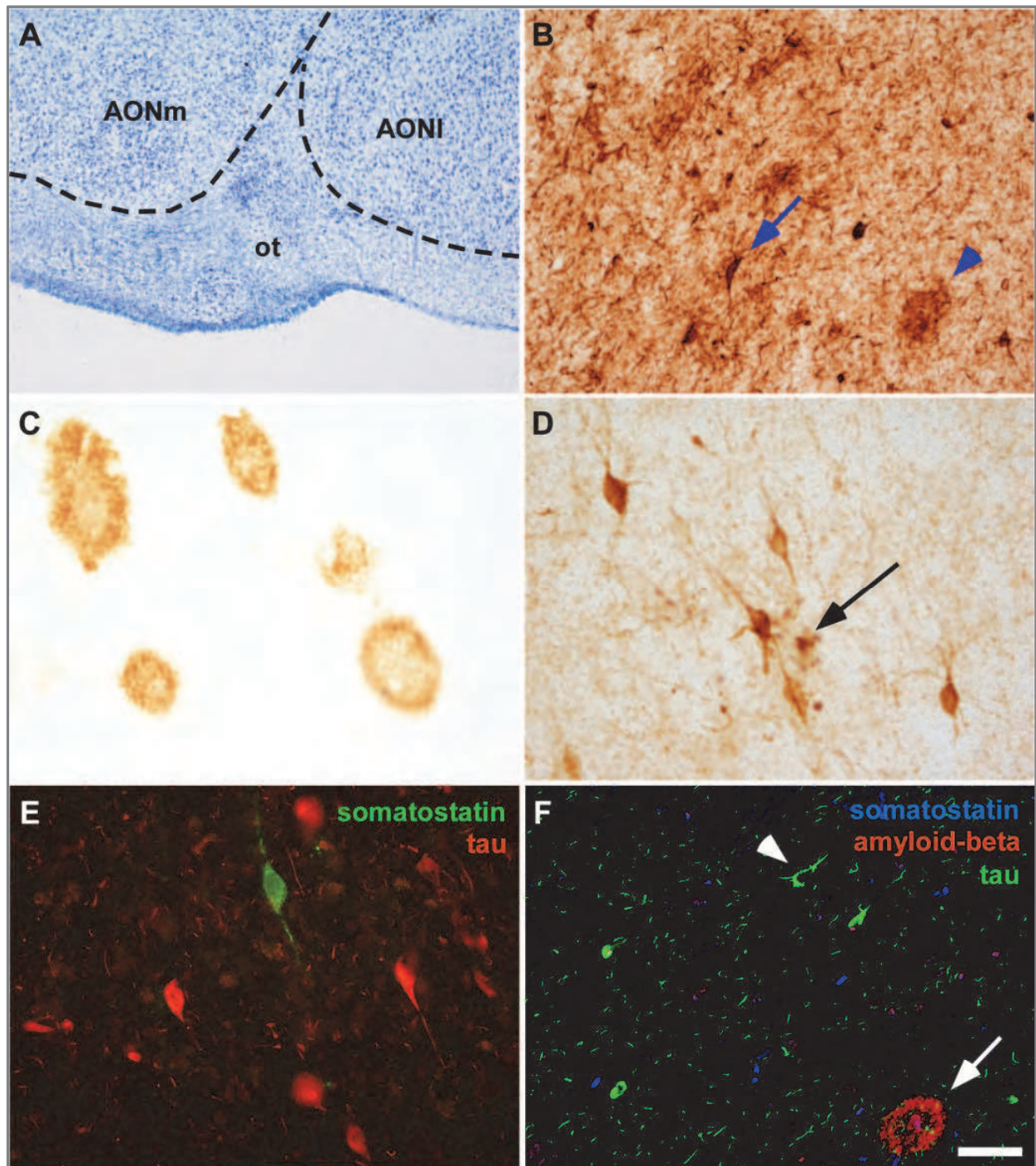


Fig. 2. Expression of somatostatin, tau and β -amyloid in the anterior olfactory nucleus (AON) in Alzheimer's disease. (A) Nissl staining of AON in the basal forebrain. (B) Immunohistochemistry of tau protein (blue arrow, dystrophic neuron; blue arrowhead, cellular debris). (C) β -Amyloid positive senile plaques in AON. (D) Somatostatin-expressing cell in the AON showing a dystrophic neuron (black arrow). (E) Double immunofluorescence for somatostatin (green) and tau protein (red). Confocal image of triple immunofluorescence for somatostatin (blue), β -amyloid (red) and tau (green). Note a neuron positive only for tau protein (white arrowhead) and a typical senile plaque (red). Scale bar: A = 400 μ m, B & F = 80 μ m, D, C & E = 40 μ m.

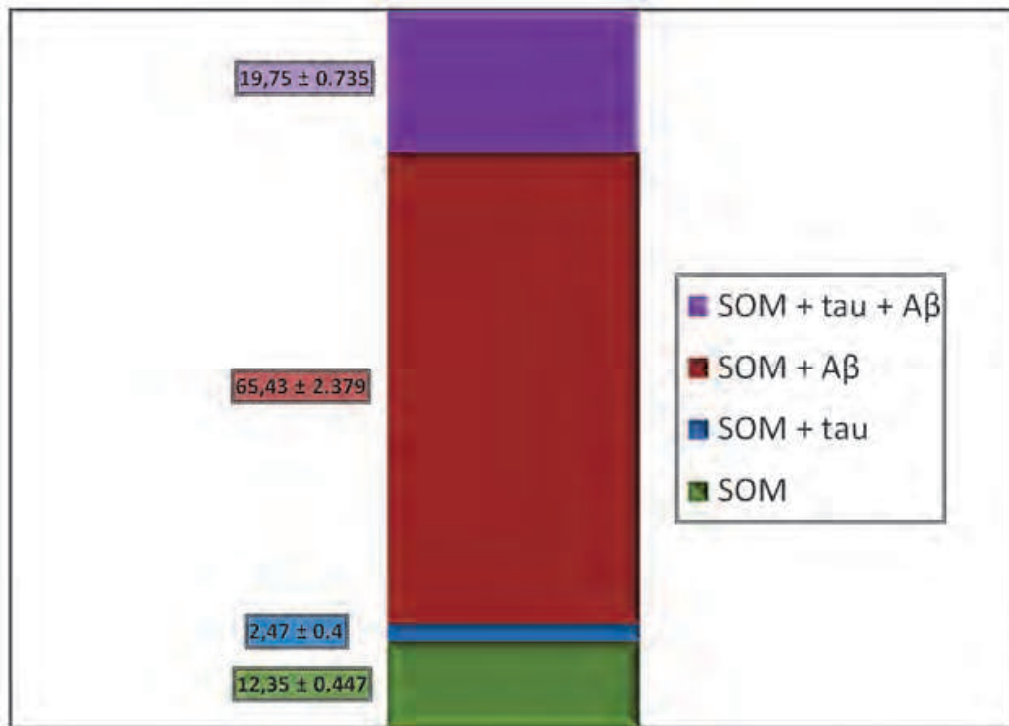


Fig. 3. Percentage of the three different types of colocalization of somatostatin-expressing cells (SOM) with tau protein (tau) and β -amyloid peptide (A β) in the human anterior olfactory nucleus.

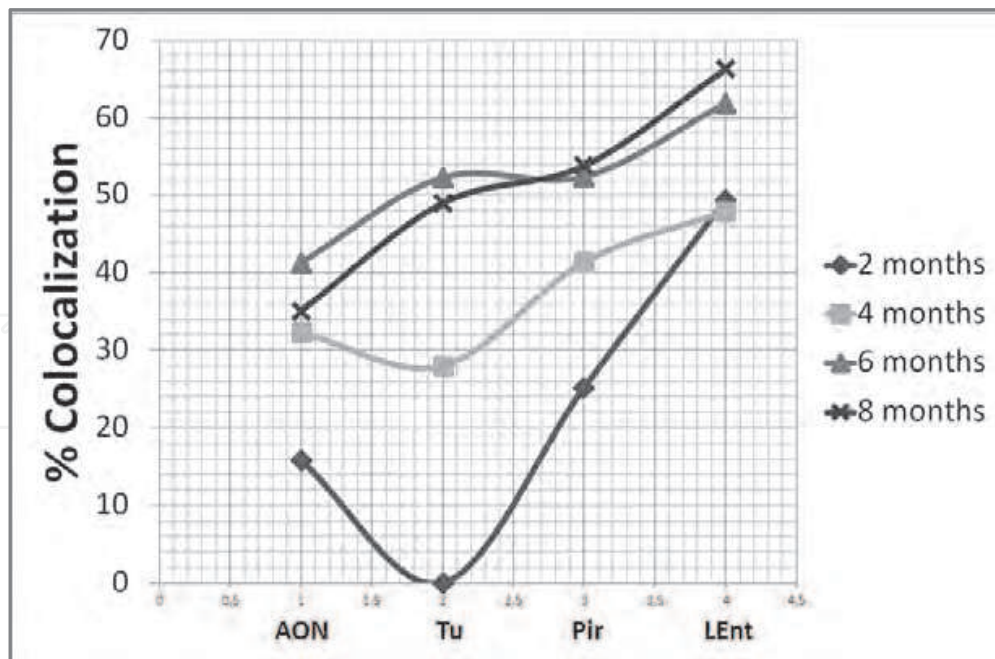


Fig. 4. Percentages of somatostatin and β -amyloid colocalization in the APPswe/PSEN1 Δ 9 mice olfactory system. Note that the external plexiform layer from the olfactory bulb is absent. AON, anterior olfactory nucleus; LEnt, lateral entorhinal cortex; Pir, piriform cortex; Tu, olfactory tubercle.

All olfactory areas showed a marked accumulation of β -amyloid deposits, but the extent of accumulation in olfactory tubercle (Tu) was less than in other areas (Fig. 5A–D). The greatest reduction in cells expressing somatostatin was seen in the external plexiform layer (EPL) (Fig. 5E,F) of the olfactory bulb, the piriform cortex (Pir) and the entorhinal cortex (Ent). In addition, the olfactory tubercle (Tu) and anterior olfactory nucleus (AON) both showed significant reductions in levels of somatostatin-positive cells. Different forms of colocalization were observed, including isolated cells (Fig. 5G), fibers and cell debris (Fig. 5H, I). Colocalization increased with age and was greater in caudal olfactory areas than in rostral areas. No colocalization was found in the external plexiform layer of the olfactory bulb where β -amyloid pathology was restricted to the granule cell layer (Fig. 5A,D) and was largely absent from the EPL.

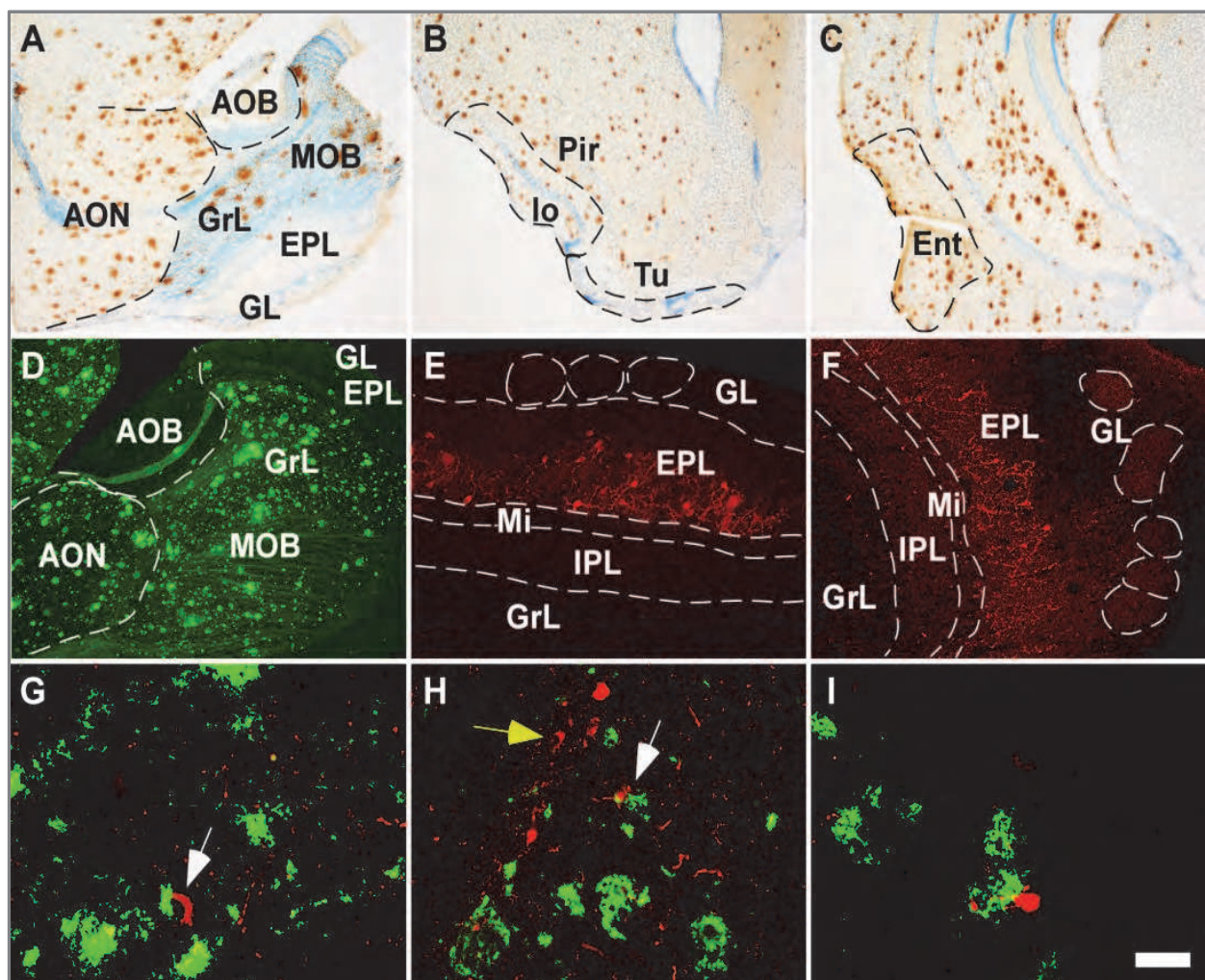


Fig. 5. Somatostatin and β -amyloid in the olfactory system of APPswe/PSEN1 Δ 9 mice. Green, β -amyloid; red, somatostatin. Immunohistochemistry for β -amyloid in the olfactory bulb (A), including anterior olfactory nucleus, piriform cortex and olfactory tubercle (B) and entorhinal cortex (C). Immunofluorescence in the olfactory bulb for β -amyloid (D) and somatostatin in a control mouse (E) and 6 months old transgenic mice (F). Confocal images demonstrating β -amyloid colocalization with somatostatin-expressing cells (G), fibers and cell debris (H, I). Scale bar: A, B, C & D = 400 μ m, E & F = 80 μ m, G & H = 40 μ m, I = 25 μ m

3.2 Calcium-binding proteins

Calcium is an intracellular second messenger that mediates physiological responses of neurons to chemical and electrical stimulation. In AD defective calcium homeostasis is thought to cause aberrant cellular metabolism and promote cell death (Heizmann & Braun, 1992, Mattson, 2007). Calcium has been related to changes in learning (Foster, 2007, Palop et al., 2003) and altered calcium regulation has been reported in AD brains before any cognitive deficits become apparent (Bezprozvanny & Mattson, 2008).

Our analysis focused on three interneuron subpopulations expressing three different calcium-binding proteins (CaBP): calbindin, calretinin and parvalbumin. All three proteins are expressed in the olfactory system, but with different distributions.

3.3 Calbindin

Most studies on calbindin D-28k have concluded that there is a general decline in levels in AD brain compared to controls (Ferrer et al., 1993, Iacopino & Christakos, 1990, Ichimiya et al., 1988).

In AD brain, calbindin D-28k is expressed widely throughout the olfactory system and is particularly abundant in key structures of olfactory processing such as the AON (Fig. 6A,B) and the piriform cortex (Fig. 6C). Especially evident is the pathological involvement of calbindin 28-Dk in the piriform cortex (Fig. 6C) where aberrant morphologies of calbindin-expressing dystrophic neuritis can be observed (Fig. 6D). Although calbindin-positive cells in the human olfactory system show some involvement with β -amyloid pathology, there was a stronger association with tau pathology (Fig. 6E, F).

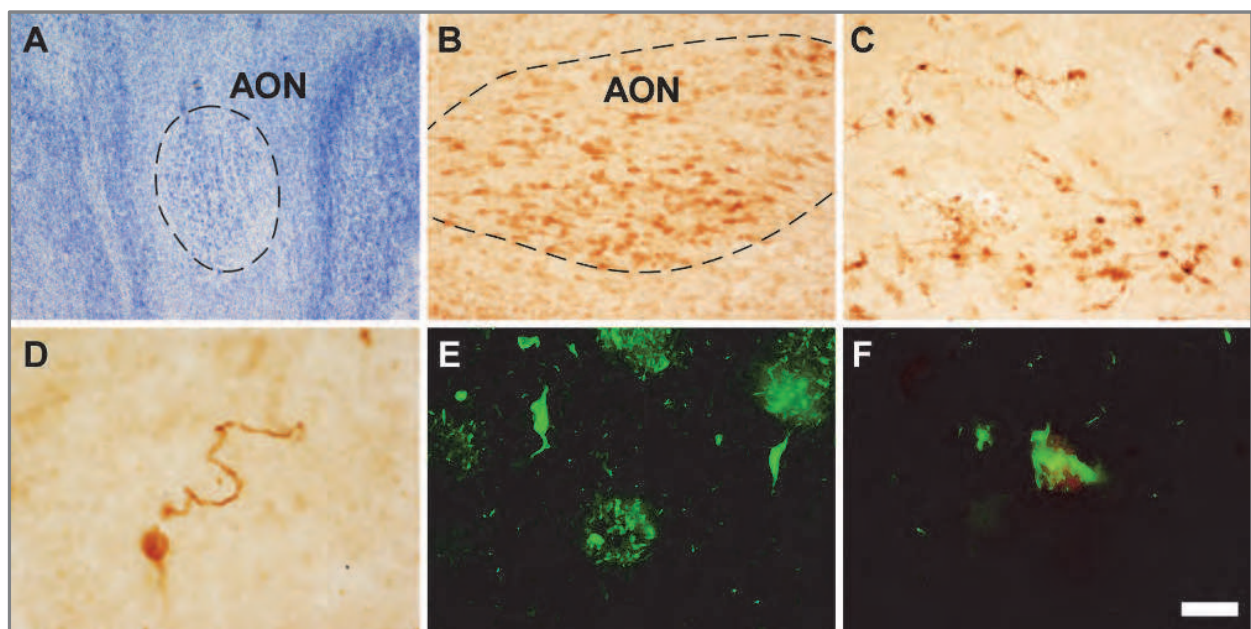


Fig. 6. Calbindin D-28k in the olfactory system of Alzheimer's disease brain. Green, tau protein and red, calbindin D-28k. (A) Nissl staining of the human anterior olfactory nucleus (AON). (B) Calbindin-expressing cell in the AON. (C) Calbindin-expressing cell in the piriform cortex (Pir). (D) Detail of a dystrophic neurite. (E) Tau pathology in Pir. (F) Calbindin-expressing cell with associated tau pathology. Scale bar: A = 160 μ m, B & C = 80 μ m, E = 40 μ m, D & F = 25 μ m.

3.4 Calretinin

Whereas calbindin D-28k is firmly associated with AD neuropathology, the involvement of calretinin in AD is more controversial (Brion & Resibois, 1994, Fonseca & Soriano, 1995, Hof et al., 1993, Sampson et al., 1997). Some authors propose that calretinin-positive cells are resistant to disease progression as a result of its capacity to buffer intracellular calcium levels. Furthermore, the potential role of calretinin in the neural basis of hyposmia remains unclear. We have studied the distribution of calretinin distribution in the human olfactory system and its involvement by tau and β -amyloid pathology.

Microscopy observations revealed that calretinin is present throughout the olfactory system. AD brain expression levels were found to be markedly reduced in olfactory areas such as AON (Fig. 7B) and Pir (Fig. 7C) relative to control brain (Fig. 7D). As with calbindin-expressing cells, calretinin-positive cells showed aberrant morphologies. In addition, these cells showed preferential involvement of tau pathology. In the olfactory bulb calretinin was found to be expressed in the periglomerular cells (Fig. 7A). It is interesting to note that sensory neurons from the olfactory epithelium send their axons to glomeruli in the olfactory bulb where they make synapses with dendrites of mitral cells. These synapses are regulated by periglomerular cells (Fig. 1). Involvement of periglomerular cells could therefore lead to dysregulation of olfactory perception at the early stages of the disease.

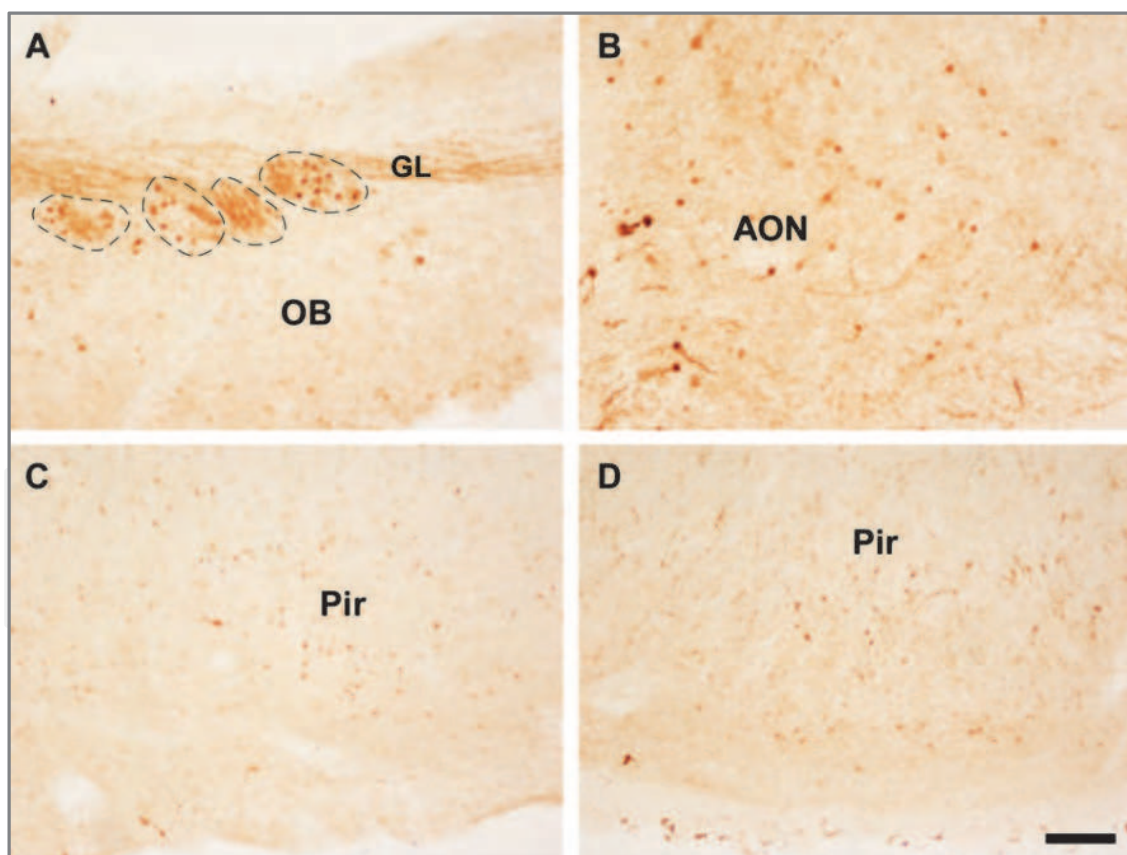


Fig. 7. Calretinin-expressing cells in the human olfactory system. (A) Periglomerular cells in the glomerular layer (GL) in the human olfactory bulb. (B) Calretinin-expressing cells in the anterior olfactory nucleus (AON). Expression of calretinin in (C) control and (D) Alzheimer's disease piriform cortex (Pir). Scale bar: A & B = 80 μ m, C & D = 400 μ m.

3.5 Parvalbumin

The third subclass of interneurons studied were those expressing parvalbumin. As with calretinin, the involvement of parvalbumin in AD is controversial. On the one hand it has been reported that there is an up to 60% decrease in the parvalbumin-positive cell population in AD hippocampus (Brady & Mufson, 1997) and entorhinal cortex (Mikkonen et al., 1999, Solodkin et al., 1996). On the other, no association was found between parvalbumin-positive cells and tau pathology in AD (Sampson et al., 1997).

In the human brain parvalbumin-expressing cells were present throughout the olfactory system and were particularly abundant in caudal olfactory areas such as piriform cortex (Fig. 8) and entorhinal cortex. In contrast to cells expressing calbindin- and calretinin, parvalbumin-positive cells showed physiological morphology, even at advanced stages of disease (Fig. 8A, B). Confocal images showed that parvalbumin-positive cells were predominantly associated with tau pathology (Fig. 8C); there was less evidence of involvement with β -amyloid pathology. As with calbindin- and calretinin-expressing cells, tau/NFT was the predominantly neuropathology associated with these calcium-binding proteins.

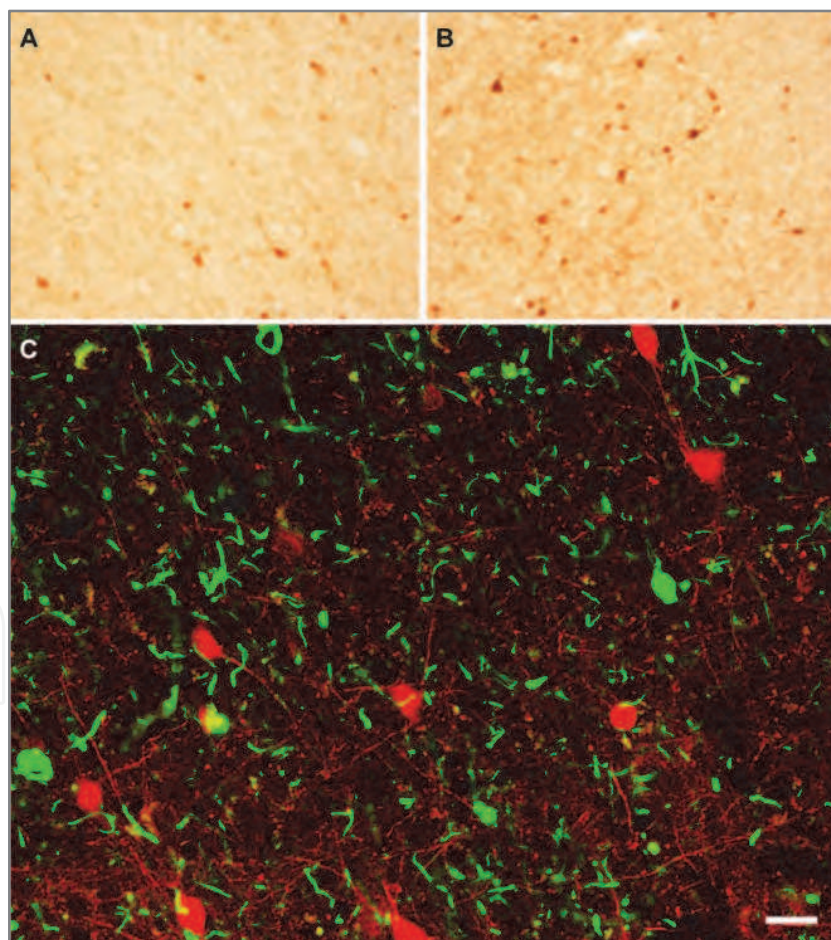


Fig. 8. Parvalbumin-expressing cells in the human olfactory system. Green, tau protein and red, parvalbumin. Immunohistochemistry of Alzheimer (A) and control (B) brain piriform cortex (Pir). (C) Confocal image of the Pir demonstrating the association of parvalbumin-expressing cells with tau pathology. Scale bar: A & B = 80 μ m, C = 25 μ m.

4. Discussion

In the present report we have studied the involvement of interneuron populations in the human olfactory system with AD neuropathology as revealed by two different disease markers: tau protein and β -amyloid peptide. Somatostatin-expressing interneurons in the olfactory system were preferentially associated with β -amyloid pathology in both AD brain and in *App^{swe}/Psen1 Δ 9* mice. By contrast, interneurons expressing different calcium-binding proteins were predominantly associated with tau pathology. In transgenic mice, cells expressing Somatostatin-cell expressing was colocalized with β -amyloid pathology in the youngest animals examined, with the exception of the external plexiform layer, and the colocalization was evident even before disease-related reduction in the numbers of somatostatin cells.

The four subpopulations of interneurons were not randomly distributed within the olfactory system. Somatostatin-expressing cells were present in the olfactory bulb but were restricted to the external plexiform layer (EPL) (Fig. 5). Somatostatin was also present in other olfactory areas, particularly in the anterior olfactory nucleus (AON). Calbindin-expressing cells were present in the olfactory system, and were particularly abundant in the AON. Calretinin-positivity constitutes a specific marker for periglomerular cells which regulate the first relay of olfactory information from the olfactory epithelium to the olfactory bulbs (Fig. 1). Calretinin-expressing cells were also abundant in the piriform cortex (Pir) and the entorhinal cortex (Ent). Parvalbumin-positive cells were more abundant in the more caudal areas studied (Pir and Ent) and were only sparsely distributed in rostral olfactory areas.

The wide presence of these interneuron populations in olfactory structures and the severe and early involvement of these regions in AD neuropathology has focused attention on the role of these cells in the pathoetiology of AD. Generalized involvement of these cells and loss of interneuron populations and/or dysregulation of their primary projection cells could underlie the olfactory deficits of AD patients. Loss of inhibitory regulation by γ -aminobutyric acid (GABA) could lead to altered firing patterns of projection neurons.

The olfactory system encompasses complex interconnections between several cortical areas (Fig. 1). Although it remains unknown whether dysfunction of specific interneuron populations in any given area could cause the olfaction deficits seen in AD, we report that there was selective association between different types of interneuron and AD neuropathology, as revealed by the two pathological markers employed in this study. However, it is not yet possible to relate these changes with specific olfaction deficits such as preferential or general anosmia, hyposmia or dysosmia. The specific contribution of each area in olfactory processing and how they are differentially affected during AD will need to be resolved before a specific olfactory test can be devised that could permit early diagnosis of AD.

5. Acknowledgements

The authors thank the Banc de Teixits Neurològics, Universitat de Barcelona-Hospital Clínic and the Banco de Tejidos/Fundación para Investigaciones Neurológicas, Universidad Complutense de Madrid, for providing the human brain samples. The authors also wish to thank the laboratory of Dr. Calvo for genotyping transgenic mice. This work was supported by the autonomous government of Castilla-La Mancha (Project N^o PEIC11-0045-4490) and by the Spanish Science and Innovation Ministry (Project BFU2010-15729).

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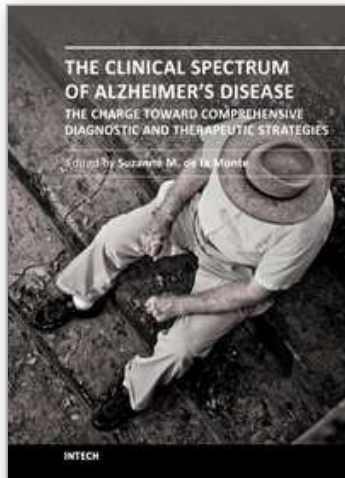
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The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

Edited by Dr. Suzanne De La Monte

ISBN 978-953-307-993-6

Hard cover, 362 pages

Publisher InTech

Published online 06, September, 2011

Published in print edition September, 2011

The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Daniel Saiz-Sánchez, Carlos de la Rosa-Prieto, Isabel Úbeda-Bañón and Alino Martínez-Marcos (2011). Neural Basis of Hyposmia in Alzheimer's Disease, *The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies*, Dr. Suzanne De La Monte (Ed.), ISBN: 978-953-307-993-6, InTech, Available from: <http://www.intechopen.com/books/the-clinical-spectrum-of-alzheimer-s-disease-the-charge-toward-comprehensive-diagnostic-and-therapeutic-strategies/neural-basis-of-hyposmia-in-alzheimer-s-disease>

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