# Review

# Olfactory dysfunction and autoimmunity: pathogenesis and new insights

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**ABSTRACT**

*Olfaction plays an important role in the perception of our environment. Smell impairment is known to be a manifestation of several autoimmune diseases. Similarities between the olfactory and immune systems and previously published human studies and animal models of autoimmune diseases account for the accumulating evidence for this observation. In this review, we will present the current literature concerning olfactory dysfunction in autoimmune diseases, discuss clinical aspects and provide new insights regarding pathogenesis and possible mechanisms.*

## Introduction

Olfaction plays an essential role in the perception of our environment. Through smelling, we communicate with our surroundings and acquire information that we utilise in our everyday life (1).

The olfactory system is able to identify specific odour molecules through a delicate physiological process that starts in the olfactory epithelium, proceeds through the olfactory nerve fibres, which converge into the olfactory nerve and bulb, and ends in olfaction-related areas in the cerebrum (2). Olfactory dysfunction (OD) is comprised of partial and complete loss of smell (hyposmia and anosmia, respectively) (3).

Recently, a complex inter-relationship between the immune and olfactory systems has been described (4, 5). OD was reported in numerous autoimmune diseases (AID), including systemic lupus erythematosus (SLE) (4, 6, 7), Sjögren's syndrome (8-10), multiple sclerosis (MS) (5, 6), systemic sclerosis (11) and idiopathic inflammatory myopathies (12). Moreover, studies support the presence of smell impairment in hereditary angioedema (13), a condition known to be associated with AID (14). OD appears to be a systemic manifestation of AID that is not necessarily limited to diseases affecting the upper respiratory tract or central nervous system (CNS). For example, smell impairment is observed in Behçet's disease. However, no correlation with nasal activity was found (15).

A thorough understanding of OD and its relation with AID is therefore needed. Herein, we review clinical aspects of smell impairment in AID, as well as provide insights into pathogenesis and possible mechanisms.

## Smell and the immune system

### *Smell, immunity and genetics*

Genes of the major histocompatibility complex (MHC) (human leukocyte activation, HLA, in humans) and olfactory receptors (ORs) appear to be physically linked. A previously published genomic study demonstrated the presence of MHC-linked ORs in 16 vertebrate species (16). Another study identified 36 human and 14 murine MHC-linked ORs loci (17).

This proximity between ORs and MHC genes may account for the fact that several animals, including mice, lizards and birds, use olfaction in order to select mates with different MHC. This evolutionary mechanism is believed to enhance the immune systems of their offspring, increase protection from pathogens and thus increase their survival rates (18-21). In mice, the vomeronasal organ (VNO, an olfactory organ) expresses class-I MHC genes called *H2-Mv*. Interestingly, higher concentrations of peptides were needed to activate the vomeronasal epithelium of *H2-Mv* knockout mice in comparison to controls, further emphasising the linkage between immune and olfaction

genetics (22). In birds, MHC-based mate selection using smell appears to vary between males and females, as males preferred non-self MHC-mates, while female birds preferred mates with similar MHC (19).

This connection between olfaction, immunity and procreation was demonstrated in humans, as well. Although lacking VNO, humans can also use smell in order to discriminate between self and non-self HLA (23). Moreover, there is evidence for body odour-based sexual selection of non-self HLA mates in humans (24). Interestingly, a recent study found a correlation between HLA-typing and odour-specific olfactory 'fingerprints' in 130 individuals, suggesting their use in future HLA screening tests (25). Therefore, HLA molecules form a bridge connecting between the olfactory and immune systems

*The immunomodulatory role of smell*

Recent studies suggest that the olfactory and immune systems interact. A good example is the olfactory bulbectomised mouse model that is used to study depression (26). Olfactory bulbectomy was found to activate the immune system. Cellular immune alterations include decrease in mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis, as well as increase in mononuclear activity and leukocytes aggregation. Humoral changes consist of increased levels of positive acute phase reactants and pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β and prostaglandin E2 (4, 27, 28). This olfactory-immune interaction appears to be bilateral, as RAG-1 (-/-) immunodeficient mice demonstrate, OD, including impaired smell and alterations in the glomerular tissue and olfactory epithelium (1).

Another study found that in a mouse model, exposure to the smell of Seirogan (a wood creosote) increased plasma levels of adrenocorticotropic hormone and cortisol, probably through activation of the hypothalamic-pituitary axis. Thus, suppressing inflammation, decreasing plasma levels of TNF-α, expression of mast cells and mucosal Immunoglobulin (Ig)A levels (29). Salivary IgA secretion was found to be affected by smell in another study, although levels were demonstrated to be increased (2). The immunomodulatory role of smell is further supported by another animal model, which found that the odour of a Japanese herbal medicine increased the levels of $CD4^+CD25^+Foxp3^+$ regulatory cells and increased survival rates of mice undergoing cardiac allograft transplantation (30).

Smell-immune interactions have also been observed in humans. An interesting study demonstrated that exposure of individuals to nostalgic odours has evoked autobiographic memories and reduced peripheral TNF-α and interferon (IFN)-γ levels (31). Odour-evoked emotions may induce the endocannabinoid system, which in turn suppresses the pro-inflammatory immune system. Yet, this remains to be determined (31). However, other studies in human subjects found different results. In one study, immune functions did not alter after exposing blinded individuals to different odours (32). Another randomised controlled trial assessed effects of lemon and lavender odours on the immune system and found that they did not alter IL-6 and IL-10 production, as well as salivary cortisol levels, as compared to no-odour (water)(33). However, significant reduction of salivary cortisol levels following exposure to orange essential oil was demonstrated in a study of 30 children during dental treatment (34). Therefore, studies concerning olfactory-induced alterations of the immune system in humans are still contradictory.

*Olfactory dysfunction is an immune-mediated process*

Several studies have demonstrated that OD is mediated by the immune system. This includes alterations in the pro-inflammatory cytokines IL-6, IFN-γ and TNF-α.

Induction of TNF-α in the olfactory epithelium of transgenic mice resulted in OD. Treatment with systemic glucocorticoids decreased local inflammation, although reversal of smell impairment was partial (35). Furthermore, knockout mice to TNF-α receptor (TNFR)-1 gene were demonstrated to have decreased inflammation in the olfactory epithelium, as well as normal electro-olfactograms (36). Knockout of the TNFR-2 gene resulted in similar results (37).

It appears that TNF-α also plays an important role in humans with hyposmia. For example, patients with type 2 congenital hyposmia were shown to have significantly increased levels of nasal mucus TNF-α, which decreased following theophylline treatment (38).

IL-6 is another pro-inflammatory cytokine mediator of smell impairment. In one study, 59 patients with hyposmia were found to have significantly increased systemic and local (oral and nasal) levels of IL-6 (39).

Finally, IFN-γ should also be mentioned in this context. Transgenic mice with induced expression of IFN-γ in the olfactory cells were shown to have abnormal electro-olfactograms with reduced response to odour molecules, although no local inflammation was observed (40). Therefore, local, as well as systemic, immune responses play a role in the pathogenesis of OD.

## Smell, neuroinflammation and neurodegenerative diseases

It appears, that neuroinflammation is important in the pathogenesis of neurodegenerative diseases, such as Alzheimer's diseases (AD) and Parkinson's disease (PD) (4). Some studies even suggest diseases like PD to have, at least partially, an autoimmune ethipathogenesis (41). Evidences for microglia activation and high levels of coefficients *K** of arachidonic acid, a neuroinflammatory marker, in the brains of AD patients, support that notion (42, 43). This is also confirmed by implicating immune-system-associated genes with neurodegenerative diseases by using genome-wide association studies (GWAS). In AD, GWAS associated the disease with Triggering Receptor Expressed on Myeloid cells 2 (*TREM2*) gene, found on immune cells in the CNS (44). Another example is genetic forms of PD, where inflammation-associated genes, such as *Parkin*, *DJ-1*, and *PINK1* were identified (45).

A connection between chronic neuroinflammation, the olfactory system and

**Table I.** Autoimmune diseases associated with olfactory dysfunction.

| Autoimmune diseases | | Animal studies | | Human studies | | | |
|---|---|---|---|---|---|---|---|
| | | Animal Model | Reference | Study Design | Number of patients | Country of publication | Reference |
| Systemic | Systemic lupus erythematosus | Mouse | (6, 7, 58, 59, 62) | CC [a] | 50 | Israel | (63) |
| | | | | CC | 85 | Portugal | (64) |
| | Sjögren's syndrome | - | - | MA [b] | 378 | UK | (9) |
| | | | | CC | 30 | USA | (76) |
| | | | | CC | 29 | USA | (77) |
| | Rheumatoid arthritis | | | CC | 101 | Germany | (78) |
| | Behçet's disease | - | - | CC | 30 | Turkey | (15) |
| | | | | CC | 50 | Turkey | (79) |
| | Systemic sclerosis | - | - | CC | 20 | Israel | (11) |
| | Idiopathic inflammatory myopathies | - | - | CC | 60 | Italy | (12) |
| | Psoriasis vulgaris | - | - | CC | 50 | Turkey | (80) |
| | Churg-Strauss syndrome | - | - | CR [c] | 1 | USA | (81) |
| | Granulomatosis with polyangiitis (Wegener's granulomatosis) | - | - | CC | 44 | Germany | (82) |
| | | | | CC | 16 | Germany | (83) |
| | | | | CC | 76 | Germany | (84) |
| | | | | CC | 9 | Germany | (85) |
| Organ-specific | Inflammatory bowel disease | - | - | CC | 59 | Germany | (86) |
| | Mikulicz's disease | - | - | CC | 44 | Japan | (87) |
| | Multiple sclerosis | Mouse | (67) | CC | 73 | Canada | (66) |
| | | | | CC | 20 | Germany | (88) |
| | | | | CC | 100 | Brazil | (68) |
| | | | | CC | 17 | UK | (89) |
| | | | | SR [d] | 865 | USA | (65) |
| | Neuromyelitis optica | - | - | CC | 3 | UK | (89) |
| | | | | CC | 10 | Germany | (90) |
| | Acute disseminated encephalomyelitis | - | - | CC | 7 | UK | (89) |
| | Giant cell arteritis | - | - | CR | 1 | UK | (91) |
| | Myasthenia gravis | - | - | CC | 30 | Turkey | (75) |
| | | | | CC | 27 | USA | (74) |
| | | | | CR | 1 | China | (72) |
| | Primary biliary cirrhosis | - | - | CC | 43 | USA | (92) |
| | Type 1 diabetes mellitus | - | - | CC | 39 | Turkey | (93) |
| | Pemphigus vulgaris | - | - | CC | 28 | Turkey | (94) |
| | Autoimmune pancreatitis | - | - | CR | 1 | USA | (95) |

[a] CC: Case-control. [b] CR: Case-report. [c] MA: Meta-analysis of 5 studies (3 cross-sectional, 1 prospective cross-sectional and observational study and 1 observational transversal study). [d] SR: Scoping review of 25 case-control studies.

neurodegenerative diseases, was recently drawn. Smell impairment is observed in early stages of PD (5) and AD (46) and other rare neurodegenerative diseases, such as Huntington's disease, frontotemporal dementia and spinocerebellar ataxia type 2 (47).

Furthermore, early pathological changes, such as the presence of neurofibrillary tangles and Lewy bodies, can be observed in the olfactory bulbs of patients with AD and PD, respectively (48, 49). In fact, involvement of the olfactory system in AD is not limited to the olfactory bulb and it also includes higher olfactory cortical levels (47).

This link between olfaction and neurodegenerative diseases affects both diagnosis and prognosis. One study, proposed using a combination of transcranial sonography of the substantia nigra and olfactory testing, in order to increase the accuracy of early PD diagnosis (50). Another study, conducted in the university of Pennsylvania, found that olfactory stress test with the use of atropine may be helpful in the diagnosis of preclinical AD (51). The diagnostic value of olfactory test in early AD was confirmed in a recent systematic review (52).

Prognosis is also affected. OD was found to predict cognitive decline in AD (46, 53), as well as PD (54). Faster disease progression, such as freezing of gait and levodopa equivalent dose, was found in PD patients with smell

impairment (55). Furthermore, a recent population-based study in Sweden found that OD is a predictor of higher mortality rates in patients with dementia (56). Therefore, this complex relationship between olfaction, the immune system and neurodegenerative diseases warrants further studied, as it may have future clinical implications.

**Smell and autoimmune diseases**

Several systemic and organ-specific AID have been associated with smell impairment (see Table I). Herein, we will elaborate on three diseases: SLE, MS and myasthenia gravis (MG).

*Systemic lupus erythematosus*

SLE is considered by many a hallmark for chronic and systemic AID. Several animal models and human studies support the notion that OD is one of its manifestations.

MRL/lpr mouse model is important in that regard. The *lpr* mutation alters transcription of FAS-ligand and results in a SLE-like disease phenotype characterised by high mortality rates, lymphoproliferation and high serum levels of autoantibodies, such as anti-nuclear antibody (ANA) (57). Using this model, researchers have demonstrated that SLE-prone mice had reduced performance when exposed to different low concentration odours, which suggested a diminished sense of smell. This also included a decreased distribution of neuroblasts into the olfactory bulb (58). Treatment of MRL/lpr lupus-prone mice with cyclophosphamide, an immunosuppressive drug, resulted in both increased sensation of attractant odours and exacerbated abnormal response to repellents (59).

Another mouse model includes intracerebra-ventricular (ICV) injection of anti-ribosomal-P antibodies. Anti-ribosomal P antibodies bind to P0, P1 and P2 ribosomal phosphoproteins (60). Their direct injection into the brains of mice was previously reported to induce autoimmune depression, while they were found to interact with different olfactory-related areas in the brain, including the hippocampus and primary olfactory piriform cortex (61). In several studies, ICV injection of anti-ribosomal P antibodies resulted in induction of neuropsychiatric SLE (NPSLE), depressive-like behaviour and smell impairment (6, 7, 62). In this model, OD was shown to involve higher cortical functions, as was evident by manganese-enhanced MRI (6). Interestingly, anti-depressive treatment with fluoxetine improved depressive-like behaviour in these mice, yet had no effect on the decreased smell (7).

OD in SLE is also confirmed by human studies. Higher rates of smell impairment were demonstrated in 50 SLE patients, as compared to healthy controls (46% and 25%, respectively. $p \leq 0.02$). Correlation between OD, disease activity and NPSLE manifestations was also seen (63).

This was later confirmed by another study, in which, self-reported anxiety and depression questionnaires were filled by 85 SLE patients and healthy controls. NPSLE patients were found to be more depressed and had higher rates of smell impairment in comparison to healthy controls and non-NPSLE patients (64).

Therefore, current evidence supports this intriguing interrelationship between SLE (especially NPSLE), depression and OD.

*Multiple sclerosis*

As mentioned above, it appears that there is a direct link between smell impairment, neuroinflammation and neurodegenerative diseases. Different studies confirm that MS, a chronic demyelinating AID that affects the CNS and is characterised by different relapsing and remissions clinical patterns, is also associated with OD (65). Rates of OD in MS patients vary between studies and range between 0–93% (65). Ethipathogenesis is intriguing, as primary olfactory receptor neurons are unmyelinated. Therefore, MS was considered by many to spare the olfactory system. However, the olfactory cortex is myelinated, which may account for this manifestation (66).

Animal models of MS consist of experimental autoimmune encephalomyelitis (EAE) mouse model. One study revealed that EAE model has had inflammation-induced alterations of transcriptional factors in the subventricular zone, which resulted in decreased neurogenesis in the olfactory bulb and OD (67).

Evidence supports OD in humans, as well. A recent review of 25 clinical case-control studies found a correlation between OD in MS patients and the following: higher Expanded Disability Status Scale (EDSS) scores, plaques in the olfactory brain, olfactory bulb and brain volumes, olfactory evoked potentials and related potentials, progressive MS, anxiety and depression and cognitive dysfunction(65). Another case-control study evaluated olfactory function of 100 MS patients using questionnaires and found that 32% of MS patients, as compared to 3% in the control group, had some degree of smell impairment. Moreover, EDSS scores higher than 4 were associated with increased rates of OD in these patients (68). Disease duration above 2 years was found to be in correlation with higher rates of OD in MS in some studies(69), although not in others(66). Therefore, it was suggested that OD in MS, much like aging, AD and PD, is caused by neurodegeneration (70).

*Myasthenia gravis*

MG is a good example of an organ-specific AID that does not involve the nasal cavity or the CNS, yet it was found to be associated with OD. It is characterised by production of autoantibodies against acetylcholine (ACh) receptors, which affects the synaptic transition of ACh in the neuromuscular junction and results in skeletal muscle weakness (71).

OD among MG patients was previously mentioned in a number of case reports (72). A systematic review revealed 10 reported studies connecting MG to smell impairment, most of which were case reports (73).

An interesting study published in 2012 found that 27 MG patients, as compared to healthy controls, had significantly decreased smell. This was shown by using the University of Pennsylvania Smell Identification Test (UPSIT). The researchers ruled out confounders, such as difficulties in sniffing and major cognitive dysfunction, using inhalation studies and Picture Identification Test

(PIT), respectively. Several associations between MG and central ACh-mediated neuronal processes, including the presence of type 3 muscarinic ACh receptors in olfactory neurons, were suggested. Yet, none were proven (74).

Similar results were demonstrated in 2015 in Turkey. Using odour identification, discrimination and threshold testing, OD was found to be significantly higher in MG patients than healthy controls ($p<0.001$). Interestingly, gustatory dysfunction was also noted (75). As ACh autoantibodies do not cross the blood-brain-barrier, the exact mechanism for OD in MG is yet to be defined (74, 75).

## Conclusion

OD is seen in a number of AID. This accounts for the close interrelationship between the immune and olfactory systems. Understanding the pathogenesis and underlying molecular and genetic mechanisms is important, as assessment of smell is often under-recognised by physicians. Better understanding will also form the basis for future diagnostic and therapeutic modalities that will include olfactory testing in patients with AID.

## References


1. RATTAZZI L, CARIBONI A, POOJARA R, SHOENFELD Y, D'ACQUISTO F: Impaired sense of smell and altered olfactory system in RAG-1(--) immunodeficient mice. *Front Neurosci* 2015; 9: 318.
2. PERRICONE C, SHOENFELD N, AGMON-LEVIN N, DE CAROLIS C, PERRICONE R, SHOENFELD Y: Smell and autoimmunity: a comprehensive review. *Clin Rev Allergy Immunol* 2013; 45: 87-96.
3. SCANGAS GA, BLEIER BS: Anosmia: differential diagnosis, evaluation, and management. *Am J Rhinol Allergy* 2017; 31: 3-7.
4. MOSCAVITCH SD, SZYPER-KRAVITZ M, SHOENFELD Y: Autoimmune pathology accounts for common manifestations in a wide range of neuro-psychiatric disorders: the olfactory and immune system interrelationship. *Clin Immunol* 2009; 130: 235-43.
5. STROUS RD, SHOENFELD Y: To smell the immune system: olfaction, autoimmunity and brain involvement. Autoimmun Rev 2006; 6: 54-60.
6. KIVITY S, TSARFATY G, AGMON-LEVIN N *et al*.: Abnormal olfactory function demonstrated by manganese-enhanced MRI in mice with experimental neuropsychiatric lupus. *Ann N Y Acad Sci* 2010; 1193: 70-7.
7. KATZAV A, BEN-ZIV T, CHAPMAN J, BLANK M, REICHLIN M, SHOENFELD Y: Anti-P ribosomal antibodies induce defect in smell capability in a model of CNS -SLE (depression). *J Autoimmun* 2008; 31: 393-8.
8. KAMEL UF, MADDISON P, WHITAKER R: Impact of primary Sjögren's syndrome on smell and taste: effect on quality of life. *Rheumatology* (Oxford) 2009; 48: 1512-4.
9. AL-EZZI MY, PATHAK N, TAPPUNI AR, KHAN KS: Primary Sjögren's syndrome impact on smell, taste, sexuality and quality of life in female patients: A systematic review and meta-analysis. *Mod Rheumatol* 2016: 1-7.
10. RASMUSSEN N, BROFELDT S, MANTHORPE R: Smell and nasal findings in patients with primary Sjögren's syndrome. *Scand J Rheumatol Suppl* 1986; 61: 142-5.
11. AMITAL H, AGMON-LEVIN N, SHOENFELD N *et al*.: Olfactory impairment in patients with the fibromyalgia syndrome and systemic sclerosis. *Immunol Res* 2014; 60: 201-7.
12. IACCARINO L, SHOENFELD N, RAMPUDDA M *et al*.: The olfactory function is impaired in patients with idiopathic inflammatory myopathies. *Immunol Res* 2014; 60: 247-52.
13. PERRICONE C, AGMON-LEVIN N, SHOENFELD N *et al*.: Evidence of impaired sense of smell in hereditary angioedema. *Allergy* 2011; 66: 149-54.
14. TRIGGIANESE P, CHIMENTI MS, TOUBI E *et al*.: The autoimmune side of hereditary angioedema: insights on the pathogenesis. *Autoimmun Rev* 2015; 14: 665-9.
15. VEYSELLER B, DOGAN R, OZUCER B *et al*.: Olfactory function and nasal manifestations of Behçet's disease. *Auris Nasus Larynx* 2014; 41: 185-9.
16. SANTOS PS, KELLERMANN T, UCHANSKA-ZIEGLER B, ZIEGLER A: Genomic architecture of MHC-linked odorant receptor gene repertoires among 16 vertebrate species. *Immunogenetics* 2010; 62: 569-84.
17. YOUNGER RM, AMADOU C, BETHEL G *et al*.: Characterization of clustered MHC-linked olfactory receptor genes in human and mouse. *Genome Res* 2001; 11: 519-30.
18. STRANDH M, WESTERDAHL H, PONTARP M *et al*.: Major histocompatibility complex class II compatibility, but not class I, predicts mate choice in a bird with highly developed olfaction. *Proc Biol Sci* 2012; 279: 4457-63.
19. LECLAIRE S, STRANDH M, MARDON J, WESTERDAHL H, BONADONNA F: Odour-based discrimination of similarity at the major histocompatibility complex in birds. *Proc Biol Sci* 2017; 284.
20. YAMAZAKI K, BEAUCHAMP GK: Genetic basis for MHC-dependent mate choice. *Adv Genet* 2007; 59: 129-45.
21. OLSSON M, MADSEN T, NORDBY J, WAPSTRA E, UJVARI B, WITTSELL H: Major histocompatibility complex and mate choice in sand lizards. *P Roy Soc B-Biol Sci* 2003; 270: S254-S6.
22. LEINDERS-ZUFALL T, ISHII T, CHAMERO P *et al*.: A family of nonclassical class I MHC genes contributes to ultrasensitive chemodetection by mouse vomeronasal sensory neurons. *J Neurosci* 2014; 34: 5121-33.
23. MILINSKI M, CROY I, HUMMEL T, BOEHM T: Major histocompatibility complex peptide ligands as olfactory cues in human body odour assessment. *Proc Biol Sci* 2013; 280: 20122889.
24. KROMER J, HUMMEL T, PIETROWSKI D *et al*.: Influence of HLA on human partnership and sexual satisfaction. *Sci Rep* 2016; 6: 32550.
25. SECUNDO L, SNITZ K, WEISSLER K *et al*.: Individual olfactory perception reveals meaningful nonolfactory genetic information. *Proc Natl Acad Sci USA* 2015; 112: 8750-5.
26. LUMIA AR, TEICHER MH, SALCHLI F, AYERS E, POSSIDENTE B: Olfactory bulbectomy as a model for agitated hyposerotonergic depression. *Brain Res* 1992; 587: 181-5.
27. MORALES-MEDINA JC, IANNITTI T, FREEMAN A, CALDWELL HK: The olfactory bulbectomized rat as a model of depression: The hippocampal pathway. *Behav Brain Res* 2017; 317: 562-75.
28. SONG C, LEONARD BE: The olfactory bulbectomised rat as a model of depression. *Neurosci Biobehav Rev* 2005; 29:627-47.
29. HIRAMOTO K, YAMATE Y, KOBAYASHI H *et al*.: Effect of the smell of Seirogan, a wood creosote, on dermal and intestinal mucosal immunity and allergic inflammation. *J Clin Biochem Nutr* 2012; 51: 91-5.
30. JIN X, UCHIYAMA M, ZHANG Q, NIIMI M: Fox smell abrogates the effect of herbal odor to prolong mouse cardiac allograft survival. *J Cardiothorac Surg* 2014; 9: 82.
31. MATSUNAGA M, BAI Y, YAMAKAWA K *et al*.: Brain-immune interaction accompanying odor-evoked autobiographic memory. *PLoS One* 2013; 8: e72523.
32. TRELLAKIS S, FISCHER C, RYDLEUSKAYA A *et al*.: Subconscious olfactory influences of stimulant and relaxant odors on immune function. *Eur Arch Otorhinolaryngol* 2012; 269: 1909-16.
33. KIECOLT-GLASER JK, GRAHAM JE, MALARKEY WB, PORTER K, LEMESHOW S, GLASER R: Olfactory influences on mood and autonomic, endocrine, and immune function. *Psychoneuroendocrinology* 2008; 33: 328-39.
34. JAFARZADEH M, ARMAN S, POUR FF: Effect of aromatherapy with orange essential oil on salivary cortisol and pulse rate in children during dental treatment: A randomized controlled clinical trial. *Adv Biomed Res* 2013; 2: 10.
35. SULTAN B, MAY LA, LANE AP: The role of TNF-alpha in inflammatory olfactory loss. *Laryngoscope* 2011; 121: 2481-6.
36. SOUSA GARCIA D, CHEN M, SMITH AK, LAZARINI PR, LANE AP: Role of the type I tumor necrosis factor receptor in inflammation-associated olfactory dysfunction. *Int Forum Allergy Rhinol* 2017; 7: 160-8.
37. POZHARSKAYA T, LIANG J, LANE AP: Regulation of inflammation-associated olfactory neuronal death and regeneration by the type II tumor necrosis factor receptor. *Int Forum Allergy Rhinol* 2013; 3: 740-7.
38. HENKIN RI, ABDELMEGUID M, KNOPPEL AB: On the mechanism of smell loss in patients with Type II congenital hyposmia. *Am J Otolaryngol* 2016; 37: 436-41.
39. HENKIN RI, SCHMIDT L, VELICU I: Interleukin 6 in hyposmia. *JAMA Otolaryngol Head Neck Surg* 2013; 139: 728-34.
40. POZHARSKAYA T, LANE AP: Interferon gamma causes olfactory dysfunction without concomitant neuroepithelial damage. *Int Forum Allergy Rhinol* 2013; 3: 861-5.
41. DE VIRGILIO A, GRECO A, FABBRINI G *et al*.: Parkinson's disease: Autoimmunity and neuroinflammation. *Autoimmun Rev* 2016; 15: 1005-11.
42. KOHL Z, SCHLACHETZKI JC, FELDEWERTH J *et al*.: Distinct pattern of microgliosis in the ol-

factory bulb of neurodegenerative proteinopathies. *Neural Plast* 2017; 2017: 3851262.
43. ESPOSITO G, GIOVACCHINI G, LIOW JS *et al*.: Imaging neuroinflammation in Alzheimer's disease with radiolabeled arachidonic acid and PET. *J Nucl Med* 2008; 49: 1414-21.
44. BOLOS M, PEREA JR, AVILA J: Alzheimer's disease as an inflammatory disease. *Biomol Concepts* 2017; 8: 37-43.
45. STOJKOVSKA I, WAGNER BM, MORRISON BE: Parkinson's disease and enhanced inflammatory response. *Exp Biol Med* (Maywood) 2015; 240: 1387-95.
46. ROBERTS RO, CHRISTIANSON TJ, KREMERS WK *et al*.: Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. *JAMA Neurol* 2016; 73: 93-101.
47. ATTEMS J, WALKER L, JELLINGER KA: Olfactory bulb involvement in neurodegenerative diseases. *Acta Neuropathol* 2014; 127: 459-75.
48. KOVACS T, CAIRNS NJ, LANTOS PL: Olfactory centres in Alzheimer's disease: olfactory bulb is involved in early Braak's stages. *Neuroreport* 2001; 12:285-8.
49. BENKLER M, AGMON-LEVIN N, SHOENFELD Y: Parkinson's disease, autoimmunity, and olfaction. *Int J Neurosci* 2009; 119: 2133-43.
50. IZAWA MO, MIWA H, KAJIMOTO Y, KONDO T: Combination of transcranial sonography, olfactory testing, and MIBG myocardial scintigraphy as a diagnostic indicator for Parkinson's disease. *Eur J Neurol* 2012; 19: 411-6.
51. SCHOFIELD PW, EBRAHIMI H, JONES AL, BATEMAN GA, MURRAY SR: An olfactory 'stress test' may detect preclinical Alzheimer's disease. *BMC Neurol* 2012; 12:24.
52. GROS A, MANERA V, DE MARCH CA *et al*.: Olfactory disturbances in ageing with and without dementia: towards new diagnostic tools. *J Laryngol Otol* 2017: 1-8.
53. DEVANAND DP, LEE S, MANLY J *et al*.: Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology* 2015; 84: 182-9.
54. FULLARD ME, TRAN B, XIE SX *et al*.: Olfactory impairment predicts cognitive decline in early Parkinson's disease. *Parkinsonism Relat Disord* 2016; 25: 45-51.
55. CAVACO S, GONCALVES A, MENDES A *et al*.: Abnormal olfaction in Parkinson's disease is related to faster disease progression. *Behav Neurol* 2015; 2015: 976589.
56. EKSTROM I, SJOLUND S, NORDIN S *et al*.: Smell loss predicts mortality risk regardless of dementia conversion. *J Am Geriatr Soc* 2017; 65: 1238-43.
57. PERRY D, SANG A, YIN Y, ZHENG YY, MOREL L: Murine models of systemic lupus erythematosus. *J Biomed Biotechnol* 2011; 2011: 271694.
58. KAPADIA M, STANOJCIC M, EARLS AM, PULAPAKA S, LEE J, SAKIC B: Altered olfactory function in the MRL model of CNS lupus. *Behav Brain Res* 2012; 234: 303-11.
59. KAPADIA M, ZHAO H, MA D, SAKIC B: Sustained immunosuppression alters olfactory function in the MRL model of CNS Lupus. *J Neuroimmune Pharmacol* 2017 Apr 11 [Epub ahead of print].
60. SHOENFELD Y: To smell autoimmunity: anti-P-ribosomal autoantibodies, depression, and the olfactory system. *J Autoimmun* 2007; 28: 165-9.
61. KATZAV A, SOLODEEV I, BRODSKY O *et al*.: Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arthritis Rheum* 2007; 56: 938-48.
62. KATZAV A, BEN-ZIV T, BLANK M, PICK CG, SHOENFELD Y, CHAPMAN J: Antibody-specific behavioral effects: intracerebroventricular injection of antiphospholipid antibodies induces hyperactive behavior while anti-ribosomal-P antibodies induces depression and smell deficits in mice. *J Neuroimmunol* 2014; 272: 10-5.
63. SHOENFELD N, AGMON-LEVIN N, FLITMAN-KATZEVMAN I *et al*.: The sense of smell in systemic lupus erythematosus. *Arthritis Rheum* 2009; 60: 1484-7.
64. CAVACO S, MARTINS DA SILVA A, SANTOS E *et al*.: Are cognitive and olfactory dysfunctions in neuropsychiatric lupus erythematosus dependent on anxiety or depression? *J Rheumatol* 2012; 39: 770-6.
65. LUCASSEN EB, TUREL A, KNEHANS A, HUANG X, ESLINGER P: Olfactory dysfunction in Multiple Sclerosis: A scoping review of the literature. *Mult Scler Relat Disord* 2016; 6: 1-9.
66. GOOD KP, TOURBIER IA, MOBERG P *et al*.: Unilateral olfactory sensitivity in multiple sclerosis. *Physiol Behav* 2017; 168: 24-30.
67. TEPAVCEVIC V, LAZARINI F, ALFARO-CERVELLO C *et al*.: Inflammation-induced subventricular zone dysfunction leads to olfactory deficits in a targeted mouse model of multiple sclerosis. *J Clin Invest* 2011; 121: 4722-34.
68. JORDY SS, STARZEWSKI AJ, MACEDO FA, MANICA GR, TILBERY CP, CARABETTA EG: Olfactory alterations in patients with multiple sclerosis. *Arq Neuropsiquiatr* 2016; 74: 697-700.
69. ROLET A, MAGNIN E, MILLOT JL *et al*.: Olfactory dysfunction in multiple sclerosis: evidence of a decrease in different aspects of olfactory function. *Eur Neurol* 2013; 69: 166-70.
70. BATUR CAGLAYAN HZ, IRKEC C, NAZLIEL B, AKYOL GURSES A, CAPRAZ I: Olfactory functioning in early multiple sclerosis: Sniffin' Sticks Test study. *Neuropsychiatr Dis Treat* 2016; 12: 2143-7.
71. GILHUS NE: Myasthenia Gravis. *N Engl J Med* 2016; 375: 2570-81.
72. CHEN Y, WANG L, ZHOU L, GAO Y: Ocular myasthenia gravis accompanied by anosmia. *J Tradit Chin Med* 2016; 36: 125-30.
73. LEON-SARMIENTO FE, LEON-ARIZA DS, DOTY RL: Dysfunctional chemosensation in myasthenia gravis: a systematic review. *J Clin Neuromuscul Dis* 2013; 15: 1-6.
74. LEON-SARMIENTO FE, BAYONA EA, BAYONA-PRIETO J, OSMAN A, DOTY RL: Profound olfactory dysfunction in myasthenia gravis. *PLoS One* 2012; 7: e45544.
75. TEKELI H, SENOL MG, ALTUNDAG A *et al*.: Olfactory and gustatory dysfunction in Myasthenia gravis: A study in Turkish patients. *J Neurol Sci* 2015; 356: 188-92.
76. WEIFFENBACH JM, FOX PC: Odor identification ability among patients with Sjögren's syndrome. *Arthritis Rheum* 1993; 36: 1752-4.
77. HENKIN RI, TALAL N, LARSON AL, MATTERN CF: Abnormalities of taste and smell in Sjögren's syndrome. *Ann Intern Med* 1972; 76: 375-83.
78. STEINBACH S, PROFT F, SCHULZE-KOOPS H *et al*.: Gustatory and olfactory function in rheumatoid arthritis. *Scand J Rheumatol* 2011; 40: 169-77.
79. AKYOL L, GUNBEY E, KARLI R, ONEM S, OZGEN M, SAYARLIOGLU M: Evaluation of olfactory function in Behçet's disease. *Eur J Rheumatol* 2016; 3: 153-6.
80. AYDIN E, TEKELI H, KARABACAK E *et al*.: Olfactory functions in patients with psoriasis vulgaris: correlations with the severity of the disease. *Arch Dermatol Res* 2016; 308:409-14.
81. TALLAB HF, DOTY RL: Anosmia and hypogeusia in Churg-Strauss syndrome. *BMJ Case Rep* 2014; 2014.
82. PROFT F, STEINBACH S, DECHANT C *et al*.: Gustatory and olfactory function in patients with granulomatosis with polyangiitis (Wegener's). *Scand J Rheumatol* 2014; 43: 512-8.
83. FASUNLA JA, HUNDT W, LUTZ J, FORGER F, THURMEL K, STEINBACH S: Evaluation of smell and taste in patients with Wegener's granulomatosis. *Eur Arch Otorhinolaryngol* 2012; 269: 179-86.
84. LAUDIEN M, LAMPRECHT P, HEDDERICH J, HOLLE J, AMBROSCH P: Olfactory dysfunction in Wegener's granulomatosis. *Rhinology* 2009; 47: 254-9.
85. GOKTAS O, CAO VAN H, FLEINER F, LACROIX JS, LANDIS BN: Chemosensory function in Wegener's granulomatosis: a preliminary report. *Eur Arch Otorhinolaryngol* 2010; 267: 1089-93.
86. STEINBACH S, REINDL W, DEMPFLE A *et al*.: Smell and taste in inflammatory bowel disease. *PLoS One* 2013; 8: e73454.
87. TAKANO K, YAMAMOTO M, KONDO A, TAKAHASHI H, HIMI T: A clinical study of olfactory dysfunction in patients with Mikulicz's disease. *Auris Nasus Larynx* 2011; 38: 347-51.
88. UECKER FC, OLZE H, KUNTE H, GERZ C, GOKTAS O, HARMS L, SCHMIDT FA: Longitudinal Testing of Olfactory and Gustatory Function in Patients with Multiple Sclerosis. *PLoS One* 2017; 12: e0170492.
89. DELUCA GC, JOSEPH A, GEORGE J *et al*.: Olfactory Pathology in Central Nervous System Demyelinating Diseases. *Brain Pathol* 2015; 25: 543-51.
90. SCHMIDT F, GOKTAS O, JARIUS S *et al*.: Olfactory dysfunction in patients with neuromyelitis optica. *Mult Scler Int* 2013; 2013: 654501.
91. SCHON F: Involvement of smell and taste in giant cell arteritis. *J Neurol Neurosurg Psychiatry* 1988; 51: 1594.
92. DEEMS RO, FRIEDMAN MI, FRIEDMAN LS, MUNOZ SJ, MADDREY WC: Chemosensory function, food preferences and appetite in human liver disease. *Appetite* 1993; 20: 209-16.
93. ALTUNDAG A, AY SA, HIRA S *et al*.: Olfactory and gustatory functions in patients with non-complicated type 1 diabetes mellitus. *Eur Arch Otorhinolaryngol* 2017.
94. MERIC A, DOGAN R, VEYSELLER B *et al*.: Evaluation of olfaction in patients with pemphigus vulgaris. *Am J Rhinol Allergy* 2014; 28: e90-4.
95. DOORECK BS, KATZ P, BARKIN JS: Autoimmune pancreatitis in the spectrum of autoimmune exocrinopathy associated with sialoadenitis and anosmia. *Pancreas* 2004; 28: 105-7.