To smell the immune system: Olfaction, autoimmunity and brain involvement

Rael D. Strous a,b, Yehuda Shoenfeld b,c,*

a Beer Yaakov Mental Health Center, PO Box 1, Beer Yaakov 70350, Israel
b Sackler Faculty of Medicine, Tel Aviv University, Israel
c Research Unit of Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel

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Abstract

Aside from its recognition and warning functions, olfaction serves many purposes in the CNS and remains one of the most important means of communication with the environment. In addition to olfactory tract input, the olfactory bulb also receives and provides input to other brain centers that modify neuronal activity. Research in the field of immunology as well as in various brain illnesses is beginning to indicate the increasing relevance of smell in pathophysiology. Much of this is based on the many intricate interactions that exist between the immune system and the nervous system, and evidence exists that there may be something unique about the olfactory system that is inextricably related to immunological function. In addition, accumulating evidence confirms the existence of olfactory dysfunction in brain disease, much of which appears at early stages including multiple sclerosis, Alzheimer’s Disease, Parkinson’s Disease, schizophrenia and depression. Such observations may further suggest that under certain circumstances, olfactory abnormalities may be associated with autoimmune conditions. Since the organization of the olfactory system is so sensitive, impairment may be noted at an early stage. This may become important in the prediction of certain brain illnesses. While preliminary evidence may suggest a role for olfaction in the management and alleviation of various disorders, investigation of its clinical relevance remains limited.

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* Corresponding author. Research Unit of Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel.: +972 3 5302652; fax: +972 3 5352855.
E-mail addresses: raels@post.tau.ac.il (R.D. Strous), Shoenfel@post.tau.ac.il (Y. Shoenfeld).

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1. Importance of smell

Smell as one of the chemical senses is critical for the sampling of the environment and to elicit information about it. Aside from its recognition and warning functions, the olfactory system serves other purposes and may be influenced in turn by many factors at the central nervous system (CNS) level. Olfaction facilitates the identification of food, partners, predators, and serves both sensual pleasure as well as warnings against danger. It thus remains one of the most important means of communication with the environment. The process however is complex. Following the initial sensory process, axons from the thousands of cells expressing the odor receptor converge in the olfactory bulb. From there, odor signals are relayed to higher cortex regions, handling conscious thought processes, and to the limbic system, generating emotional context [1]. These include a multitude of projections including the amygdala, septal nuclei, pre-pyramidal cortex, the entorhinal cortex, hippocampus and the subiculum, many of which form the limbic system, and are thus concerned with motivation, emotion and memory [2]. Projections also reach the thalamus and the frontal cortex for recognition. Many of these tracts are bidirectional thus producing a very interactive and dynamic system.

As discovered by Linda Buck and Richard Axel (2004 Nobel Prize awardees), mammals usually have about 1000 genes for odor receptors of which only 347 code for functional odor receptors [3]. It is believed that the human being can smell between 4000 and 10,000 different odors. Furthermore, each odorant appears to activate a unique set of olfactory receptors which is known as its “signature”. Each olfactory receptor gene codes for a receptor that only recognizes a few odorants, duly noted when an increased expression of a single gene led to a greater sensitivity to a small subset of odorants [4]. Others however have reported that each olfactory neuron expresses only one olfactory receptor gene, an important finding since this knowledge could lead to the unraveling of any “code” governing smell if known which receptors are activated by which odors [5]. Smell remains a complicated function since in addition to the input at the olfactory tract, the bulb also receives input from other brain centers that modify this neuronal activity. Information regarding smell is readily stored in long-term memory and has strong connections to emotional memory. While most attention at the molecular biology level has focused on genetic investigation, the burgeoning field of immunology research is beginning to indicate relevance of smell for immunological investigation. Considering the growing understanding of the complexity of the olfactory system, this is not surprising.

2. Smell, the immunological system and autoimmunity

Many intricate interactions exist between the immune system and the CNS. In insects for example, non-infected honeybees whose immune systems are challenged by a non-pathogenic immunogenic elicitor, lipopolysaccharide (LPS), have reduced abilities to associate an odor with sugar reward in a classical conditioning paradigm. Effects on the immune response therefore may affect olfaction and subsequently general behavior and memory formation [6]. Since olfaction appears to play such a central role in many aspects of central nervous function it may be assumed that when immunological function is impaired or disrupted such as in processes of autoimmunity (of which there are many mechanisms including illness such as HIV), olfaction would be affected in various degrees including at early illness stages. It may therefore be suggested that if olfaction is impaired in such a fashion, and it is known that olfaction may be affected by autoimmune processes, then these other illnesses may be associated with impaired autoimmunity. This may indirectly shed light on aspects of pathophysiology of various brain illnesses, information that may not necessarily have been available had olfaction not been impaired.

Olfactory bulbectomy is commonly used as an animal model of depression. Unexpectedly however, a variety of abnormalities may be observed in the olfactory bulbectomized rodent and appear in a number of brain regions as a consequence of disrupted neuronal connections (reviewed in [7]). The olfactory system thus serves a role in central nervous system function above and beyond that of smell. Olfactory bulbectomy also leads to numerous immune changes. These include reduced neutrophil phagocytosis, lymphocyte mitogenesis, lymphocyte number and negative acute phase proteins, increased leukocyte adhesiveness/aggregation, monocyte phagocytosis, neutrophil number and positive acute phase proteins (reviewed in [8]). In addition, enhanced nocturnal secretion of corticosterone occurs in olfactory bulbectomized rats (this is normally suppressed by dexamethasone) [8]. These processes indicate that there may be something unique about the olfactory system that is inextricably related to immunological function. In ways often unexpected, perturbations in the immunological system and/or the olfactory system may be significant to each other.

Furthermore, it appears that associated with the status of olfactory bulbectomy, there is T-Helper cell type 1 and T-Helper cell type 2 immune activation. This implies the existence of a state consistent with features of an autoimmune process. Evidence for such a process may be found in various changes in humoral immunity in
olfactory bulbectomized rats. After bulbectomy, increases in serum IL-1β concentration and PGE2 may be observed (reviewed in [7]). In contrast, basal anti-inflammatory cytokine IL-10 concentration is suppressed [7]. Interestingly an increase in the serum IL-1β and PGE2 concentrations in depressed patients have been correlated with activation of HPA axis and dysfunction of central noradrenergic function [9,10]. Furthermore, rats receiving an LPS challenge to activate inflammatory response following bulbectomy indicate greater increases in several brain regions of early gene expression (c-fos), the prostaglandin receptor (EP4), IγB, TNF-α and CRF [7]. Other studies have found that the activation of inflammatory system in olfactory bulbectomized rats may be related to the hyper-secretion of corticosterone and other immune modulators, further suggesting an autoimmune association with the process.

A further body of research has noted that odorant inhalation can regulate skin immune reactions and that certain odorants can mitigate the effects of stress on skin immune reactions. The fragrance of valerian oil for example downregulates stress-induced plasma corticosterone levels [11]. Regulation of serum cytokine levels has been hypothesized to be the mechanism of the regulation with suppression of interleukin-12 by odorants that downregulate contact hypersensitivity reactions [11]. In a further remarkable study on the subject, the effects of odor on mast cell substance P production were examined (see Fig. 1). While stress causes mast cell activation via an increase in substance P, this effect of stress may be suppressed by inhalation of the odor 1,3-dimethoxy-5-methyl benzene (DMMB) (soft tea-like fragrance). Odorants therefore protect stress-induced mast cell activation by blocking the induction of substance P. This shows that odorants may modulate immune reactions in the skin. This response is important since substance P activates skin mast cells and induces the release of prostaglandin D2, histamine, and leukotriene B4, all with central influences on immune function [12]. Furthermore, the activation of suppressor T lymphocytes induced in mice by stress is blocked by the inhalation of various odorants. This response however could be blocked by procaine administration to olfactory cells [13]. Others have also noted that stressor-related odors may have various effects on immunosuppression (e.g. [14]).

3. Importance of smell in processes of brain disease

Several bodies of research confirm the existence of olfactory dysfunction in brain disease, much of which appears at very early stages. One prominent illness where this phenomenon has been commonly described is multiple sclerosis (MS). Patients often exhibit significantly

![Diagram](image-url)
low scores on the University of Pennsylvania Smell Identification Test (UPSIT), which uses microencapsulated odors released when scratched with a pencil. The UPSIT was abnormal in cases even when the visual evoked potential (VEP) was normal [15]. Interestingly, although smell changes are rarely reported by patients with MS, olfaction is often impaired and may be correlated with severity of neurological impairment [16]. Moreover, correlations have been demonstrated between magnetic resonance measures of lesion load in the white matter of the olfactory brain region and smell loss. These findings support the proposition that the extent and severity of MRI abnormalities in specific brain regions of MS are related to the presence of selective neurological and neuropsychological impairment [17]. In addition, it has also been demonstrated that a number of MS patients suffer from olfactory loss which is correlated with plaque activity within olfactory-related central brain regions such as within the inferior frontal and temporal lobes, but not within the rest of the brain [18]. Since MS is well established as an autoimmune illness, such observations strengthen the theory that under certain circumstances, olfactory abnormalities may be associated with autoimmune dysfunction.

It is also important to note that impaired olfaction in MS has been observed to be associated with symptoms of anxiety and depression [16]. Since this is a clear association between symptoms related to an autoimmune illness, the observations may come to shed some light on the potential association between mood disorders and autoimmunity, in addition to the association with olfactory disorders and autoimmunity. Interestingly as mentioned above, the olfactory bulbectomized rat has been proposed as an animal model of depression with several behavioral changes observed following bilateral olfactory bulbectomy [8]. These changes are also associated with perturbations in noradrenergic, serotonergic, cholinergic, gamma-aminobutyric acid (GABA)-ergic and glutamatergic neurotransmitter systems. A variety of antidepressants demonstrate antidepressant-like activity in this rat model (reviewed in [8]). Moreover in depression an increase in serum IL-1β and PGE2 concentrations has been associated with HPA axis activation and abnormality of central noradrenergic function [9,10]. These findings further substantiate the olfactory bulbectomy model of depression in which similar changes are present as described above.

Olfactory dysfunction is also an early and frequent symptom noted in Parkinson’s disease (PD). These olfactory deficits in Parkinson’s disease extend to abnormalities of odor detection, differentiation and identification [19]. While it remains unclear precisely what accounts for this early and significant loss of smell in Parkinson’s disease, it is clear that the phenomenon is not related to loss of dopaminergic neurons in the olfactory bulb since postmortem examination of the olfactory bulb indicates a doubling of dopaminergic neurons in this region relative to age matched controls. Rather, as suggested by the Braak staging system of Parkinson’s disease, Lewy bodies develop in this area prior to their evolution in the substantia nigra and the anterior olfactory system may be one of the earliest induction sites of the neuropathological abnormalities of the illness [20].

Abnormalities in the sense of smell in patients suffering from Alzheimer’s disease (AD) and vascular dementia also remain well described. Both illnesses demonstrate raised olfactory thresholds and impaired odor identification [21]. Electrophysiological results confirm findings of olfactory dysfunction in patients with Alzheimer’s disease and preclinical Alzheimer’s disease [22]. However it has also been reported that odor identification is impaired early in Alzheimer’s disease and may be more influenced by cognitive status than by acuity of odor detection, a function not altered until later in the disorder [23]. Thus considering this pattern of hyposmia in Alzheimer’s disease it may be suggested that these olfactory deficits are secondary and even a later cognitive deficit feature of the illness. In normal aging, some of the process occurs as well with an age-dependant decline in olfactory discrimination. A relatively recent study indicated that significant activation in aged adults takes place in all the olfactory brain structures that are activated in young adults, but with lower activation volume and intensity [24]. Interestingly, effects on smell in the elderly are known to affect appetite. Along these lines it may be hypothesized that smell may affect other illnesses targeting appetite in particular such as anorexia nervosa and bulimia. While speculative, and bearing in mind effects of the olfactory system on immunological processes as discussed above, it may be hypothesized that anorexia and bulimia nervosa may demonstrate evidence of immunological or autoimmune abnormalities. This has been shown to be the case in at least one study where a majority of patients with anorexia nervosa (AN) and bulimia nervosa (BN) demonstrated autoantibodies reacting with alpha-melanocyte-stimulating hormone (alpha-MSH) or adrenocorticotropic hormone, which are melanocortin peptides involved in appetite control and the stress response. In addition, core psychobehavioral abnormalities characteristic for eating disorders may be correlated with levels of autoAbs against alpha-MSH, suggesting that AN and BN may be associated with autoAb-mediated dysfunctions of primarily the melanocortin system [25].
In addition to the above neurological diseases, olfactory impairment may be prominently noted in several psychiatric illnesses. For example, approximately one-third of patients with a schizophrenia spectrum disorder have a measurable olfactory identification deficit at first episode. Smaller olfactory bulb volumes in schizophrenia have been observed implying that patients exhibit structural olfactory deficits as well as functional olfactory deficits [26]. Furthermore, while nonpsychotic family members of patients with schizophrenia had significantly higher mean UPSIT scores than psychotic family members, they are impaired relative to healthy controls [27] and have lower olfactory bulb volumes than controls [26]. Good et al. [28] recently observed that at first-episode of psychosis UPSIT scores can be used to identify patients at risk for persistent negative and disorganized/cognitive symptoms. In a further investigation, independent relationships of Smell Identification Test scores to social drive and intelligence in schizophrenia have been described suggesting common neural substrates for low social drive and smell impairment in schizophrenia. A brief smell identification test has been developed in an attempt to discriminate between deficit and non-deficit schizophrenia [29] and associations have been described between olfactory deficits and eye tracking abnormalities [30] and aspects of neuropsychiatric dysfunction (WCST and WAIS-R performance) [31]. A strong relationship exists between olfactory identification scores and duration of illness, implying that olfactory abilities decline progressively over the course of the disorder [32]. Olfactory identification deficits observed in patients with schizophrenia appear to reflect abnormalities of brain regions involved in olfactory pathways and are not a function of task complexity [33]. Since olfactory processing is mediated by limbic neuroanatomical structures implicated in the pathophysiology of schizophrenia, it has been widely assumed that olfactory deficits in schizophrenia reflect disturbances of cortical or subcortical brain areas prominently present in the illness [32]. This may not be the sole basis for olfactory deficits and the possibility remains that in schizophrenia, as well as in the above-mentioned neuropsychiatric syndromes, immunological impairment may play a role.

4. Smell as a predictor of brain disease

The olfactory system serves a central sensory function and the development of new olfactory neurons in fine olfactory discrimination may have developed in order to maintain dynamic control over the sense of smell. This is essential for animals for which smell is absolutely critical for their functions of survival as well as in humans where, as discussed, the olfactory system is intricately connected with a multitude of CNS networks. Plasticity in this system is often required and is observed such as in pregnancy during which a major increase in neurogenesis occurs in these regions. Novel odors may also promote the development of new olfactory interneurons [34]. Thus the olfactory system is extremely dynamic and receptive to stimuli. These properties also open up the system to multisystem impairment if problems were to develop. Since the organization is so sensitive, impairment is noted at an early stage. This may become especially important in the prediction of certain brain illnesses such as multiple sclerosis, Alzheimer’s disease and Parkinson’s Disease. The phenomenon may extend to other brain illnesses which have aspects of autoimmune dysfunction associated with their pathophysiology including psychiatric illnesses such as schizophrenia and depression. With respect to schizophrenia, Good et al. [28] suggest the clinical utility of assessing patients for olfactory identification deficits early in the course of a psychotic disorder which may be predictive and a marker of future illness subtypes characterized by negative and cognitive/disorganized symptoms rather than positive or anxiety/depression symptoms.

Thus, performance, or rather lack of performance on various olfactory testing paradigms may serve as predictor of later brain disease. For example, the predictive utility of olfactory identification deficits in patients with mild cognitive impairment has been assessed for follow-up diagnosis of probable Alzheimer’s disease. Olfaction scores were shown to be lower in patients with mild cognitive impairment than in healthy subjects. Of seventy-seven patients followed up over 2 years, 19 were diagnosed with Alzheimer’s disease. Subjects with low olfaction scores, and subjects with low olfaction scores, who reported no problems with their smell abilities, were more likely to develop Alzheimer’s disease. It was thus suggested that olfactory identification deficits, particularly when accompanied with lack of awareness of the deficits, may serve as an early diagnostic marker for Alzheimer’s disease [35]. Based on these and other findings, namely that impaired odor identification in individuals without overt dementia may be associated with an Alzheimer’s disease-like memory impairment and cognitive decline, it has been proposed that olfactory deficits may be a specific harbinger of future clinical Alzheimer’s disease dementia, deficits consistent with known hierarchical spread of preclinical pathology. Aside from the contribution to the understanding of illness at the pathophysiological level, these observations are important as early diagnosis is of critical importance for pharmacological management.
With respect to the development of Parkinson’s disease, Ponsen et al. [20] observed that idiopathic olfactory dysfunction in asymptomatic relatives (parents, siblings, or children) of Parkinson’s disease patients is associated with at least a 10% increased risk of developing Parkinson’s disease. Olfactory testing thus may be considered as an early diagnostic tool for the disease [36].

5. Olfaction, brain disease, the immune system and treatment

Considering the above discussed interaction between olfactory and immunological systems as well as the prominence of olfactory abnormalities in brain disease, it may be suggested that olfaction may come to play a role in the management and alleviation of various disorders. This is in addition to the utility of olfaction as a potential predictor of future brain illness and illness course in certain illnesses. While psychotropic and CNS effects of odorants have been minimally studied, in the early 1970s, Rovesti and Colombo [37] classified odorants as either CNS stimulants or depressants and considered them as possible tools in the management of mental disorders. Smell, or more precisely fragrance, is also known to directly affect a variety of neurotransmitters. While effects of fragrance inhalation are not clearly understood and may involve a range of activity, it has been proposed that the phenomenon is mediated by means of the autonomic system in general and the sympathetic system in particular [38]. Effects of smell on EEG have also been described [39]; however, investigation of the clinical relevance of the association remains limited and therefore poorly understood.

One interesting illustration of the potential of this paradigm being used in the management of illness is that of the use of fragrance in the treatment of depression and its associated effects on immune function. More specifically, citrus (lemon) fragrance has been shown to restore stress-induced immunosuppression in rodent models. Since dysregulation of immune function in many cases may be associated with depression, Komori et al. [40] attempted to manage mood by stimulation of the olfactory system with the aid of citrus fragrance. Remarkably they noted that doses of antidepressant medication necessary for the treatment of depression could be markedly reduced following augmentation with citrus fragrance. While the precise mechanism for the improvement with the lemon-odor remains unclear, they hypothesized that treatment with the fragrance normalized aspects of immune and neuroendocrine function leading to its positive effect. In addition, both anatomical and physiological evidence exists indicating the existence of olfactory pathways projecting to brain regions which may be associated with pathophysiology and amelioration of brain illnesses [40].

In conclusion, olfaction is becoming known as a central “player” in the pathophysiology of various brain disorders. Whether impaired olfaction in this manner represents an independent process or rather is related to any underlying illness remains incompletely understood. In addition, smell may play a role in the prediction of the future expression of brain illness manifestation and illness course. While the role of the neuroendocrine system has most frequently been associated with olfactory function and its interaction with CNS function, the role of the immune system and factors of autoimmunity in these illnesses are becoming issues to be considered as well. Further research is mandated in order to definitively determine the role of olfaction in this manner and to elucidate any means of further using the olfactory system and its immune system associations in order to understand, predict and manage these illnesses.

Take-home messages

- The olfactory system serves many purposes in the CNS including prominent interactions with the immune system.
- Recent investigation confirms the significant association of olfactory impairment with various brain illnesses and possible autoimmune conditions.
- Several examples exist including manipulation of fragrances leading to positive effects in the mitigation of stress, skin immune reactions and depression.
- Since olfactory impairment in several brain diseases appears at early stages, olfaction may serve as a predictor of various illness manifestations.
- Preliminary evidence suggests a role for olfaction in the management of various disorders.

References


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