The myth and reality of CNS involvement in SLE

Yehuda Shoenfeld

MD, FRCP, MaACR

Bergamo 25 3 15

Clinical Immunology
The Official Journal of the Clinical Immunology Society

Featured Review
Autoimmune Pathology in Relation to Neuro-Psychiatric Disorders

The interconnectivity of the smell and the immune system
The role of smell

- Identify food.
- Distinguish between healthy and diseased.
- Choose sexual mates.
- Survival.

Smell and the immune system

Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIg and biological validation of clinically relevant genes

Raghavan Raju and Marinos C. Dalaks

Brain 2005; 128:1887-96

1. Microarray experiments followed by real-time PCR and immunohistochemistry on muscle biopsies obtained before and after therapy from patients with dermatomyositis (DM) who improved and patients with inclusion body myositis (sIBM) who did not improve after controlled trials with 3 monthly intravenous immunoglobulin (IVIg) infusion.

2. Genes markedly downregulated in DM, but not sIBM, were interleukin 22, Kallman syndrome I (KAL I), an adhesion molecule shown for the first time in muscle, ICAM-I, complement C1q, and several structural protein genes.

3. The improved muscle of DM, but not sIBM, showed up regulation of chemokines CXCL 9 and CXCL11, and several immunoglobulin-related genes, suggesting an effect on muscle remodeling and regeneration.

Yehuda Shoenfeld, MD, FRCP.
Goya 18th century
ACR case definitions for NP 1999 syndromes in lupus

<table>
<thead>
<tr>
<th>CNS manifestations</th>
<th>PNS manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic Meningitis</td>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Autonomic disorder</td>
</tr>
<tr>
<td>Demyelinating disease</td>
<td>Mononeuropathy single/multiplex</td>
</tr>
<tr>
<td>Headache</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>Neuropathy, cranial</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>Plexopathy</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td></td>
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<tr>
<td>Cognitive dysfunction</td>
<td></td>
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<tr>
<td>Mood disorder</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
</tbody>
</table>
ACR neuropsychiatric SLE syndromes

Acute inflammatory demyelinating polyradiculopathy (Guillain–Barré)
Aseptic meningitis
Autonomic disorder
Cerebrovascular disease
Demyelinating syndrome
Headache
Mononeuropathy (single/multiplex)
Movement disorder (chorea)
Myasthenia gravis
Myelopathy
Neuropathy, cranial
Plexopathy
Polyneuropathy
Seizure and seizure disorders
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorders
Psychosis
Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients

Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y.
Sem Arth Rheum 34: 501-537, 2004
Brain-specific Abs included:
1) anti-neuronal Abs,
2) brain-reactive Abs (BRAA),
3) anti-human N-methyl-D-aspartate receptor Abs (NMDA),
4) anti-microtubule-associated protein 2 Abs (MAP-2),
5) anti-neurofilament Abs (ANFA),
6) anti-ganglioside Abs (AGA),
7) anti-central nervous system tissue Abs,
8) anti-brain-synaptosomal Abs,
9) anti-triosephosphate isomerase (TPI) Abs,
10) anti-glial fibrillary acidic protein (GFAP) Abs,
11) anti-serum -lymphocytotoxic Abs

Systemic Abs included:
12) anti-phospholipids
13) lupus anticoagulant (LAC),
14) anti I B2GPI Abs,
15) anti-ribosomal P Abs
16) anti-Ro Abs,
17) anti-Sm Abs,
18) anti-endothelial Abs (AECA),
19) anti-PR3/C-ANCA, Abs,
20) anti-Nedd5 Abs.
Anti-NMDA (N-methyl-D-aspartate) receptor (NR2) antibodies in SLE

Subset of anti-dsDNA ab

↓

NMDA receptor (NR2)

De Giorgio et al. Nat Med 2001; 7: 1189-93

NMDA R peptide immunized mice

↓

Anti-NMDAR ab

→ No neuronal damage

+LPS

Damage in hippocampus: cognitive dysfunction

+EPF

Damage in amygdala: behavioral disorder
Huerta et al. PNAS 2006; 103: 678-683
dsDNA

- Laminin
- Histones
- Nucleosom
- α-actinin
- Fibronectin
- Ro/SSA
- Lipoprotein lipase
- anti-C1q
- Ribosomal-P
- Vimentin
Anti-Rib P in SLE

- More than 100 studies - specificity >90%
- Sensitivity 10 – 40% (geographical variable)
- 27.4% anti-Rib-P antibody positive SLE patients are anti-dsDNA negative and anti-Sm negative.
- Some studies have shown that anti-Rib-P correlates with SLE disease activity
- Controversy: anti-Rib-P antibodies are associated with internal organ damage (CNS, kidney, liver) or feature (NPSLE).

ANTI-P: Lupus Psychosis /Depression (P/D)

ASSOCIATION

Bonfá et al., 1987.
Anti ribosomal P antibodies and central nervous system (CNS) disease in patients with SLE

- Anti-P antibodies occurred with high prevalence in lupus psychosis and antibody level varied with the clinical activity of the psychosis.
  
  Bonfa E Elkon EK,A@R  29;981,1986

- Some controversy about this association.
  
  Ebert T, Chapman J, Shoenfeld Y. Anti-ribosomal P-protein and its role in psychiatric manifestations of SLE: myth or reality? Lupus 14: 571-575, 2005
# Association between anti-ribosomal P protein antibodies and neuropsychiatric SLE: cross-sectional vs. prospective studies.

<table>
<thead>
<tr>
<th>Cross-sectional studies</th>
<th>Longitudinal or prospective studies</th>
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<tbody>
<tr>
<td>Golombek SJ, et al. 1986</td>
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<tr>
<td>Van Dam A, et al. 1991</td>
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<td>Schneebaum AB, et al. 1991</td>
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<td>Teh LS, et al. 1992</td>
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<td>Nojima Y, et al. 1992</td>
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<td>Press J, et al. 1996</td>
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<td>Arnett FC, et al. 1996</td>
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<td>Georgescu L, et al. 1997</td>
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<td>Tzioufas AG, et al. 2000</td>
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<td>Almeida D, et al. 2002</td>
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<td>Gerli R, et al. 2002</td>
<td>No</td>
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<td>Karassa FB, et al. 2006</td>
<td>No</td>
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<td>Abdel-Nasser AM, et al. 2008</td>
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<td>Haddouk S, et al. 2009</td>
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Ghirardello A, Doria A, Lupus 2009:
### Relationship between Abs to P ribosomal proteins and clinical variables in 219 SLE patients: multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE (B)</th>
<th>Wald</th>
<th>P</th>
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<tbody>
<tr>
<td>Age at onset</td>
<td>0.047-</td>
<td>0.022</td>
<td>4.560</td>
<td>0.033</td>
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<tr>
<td>Psychiatric disorders</td>
<td>2.276-</td>
<td>0.924</td>
<td>6.072</td>
<td>0.014</td>
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<tr>
<td>Malar rash</td>
<td>0.819-</td>
<td>0.365</td>
<td>5.043</td>
<td>0.025</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>1.200-</td>
<td>0.511</td>
<td>5.517</td>
<td>0.019</td>
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</table>

A prospective longitudinal analysis of anti-P antibody level fluctuations and the occurrence of neuropsychiatric (NP) manifestations during follow-up in 2 representative SLE patients (A, B).

Ghirardello A, Doria A, Lupus 2009:
Associations of anti-ribosomal P protein antibodies with neuropsychiatric and other manifestation of systemic lupus erythematosus

Abdel-Nasser AM et al
Clinical Rheumatology 2008; 27:1377-85

- 26 patients had one or more NP manifestations. Depression (59.4%), headache (46.9%) and cognitive dysfunction were the commonest NPSLE syndromes.
- aRP positive in seven (21.9%) patients, all of whom had one or more NPSLE syndromes.
- Patients with psychiatric manifestations in general and mood disorders in particular had significantly higher mean titers of aRP than patients without these disorders (p< 0.05).
Depression is an early disease manifestation in lupus-prone MRL/lpr mice

Gau HX et al
Journal of Immunology 2009; 207: 45-56

- Depression was significantly correlated with titers of autoantibodies against DNA, NMDA receptors and cardiolipin.
Anti P ribosomal can induce depression in an animal model.
Anti P ribosomal can induce depression in an animal model.
Affinity purification of anti-P-Riobosomal

Loading serum
16 hours at 4°C

Elution with HCl-glycine

Anti-P-ribo-Sepharose

The Reichlins

Purified anti-P ribosomal Abs

mg/ml 6
## Behavioral Testing: Staircase

- **# of stairs climbed**
- **# of rearing movements**

<table>
<thead>
<tr>
<th></th>
<th>Num. of stairs Aver</th>
<th>Rearing Aver</th>
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<tbody>
<tr>
<td>Contr.</td>
<td>8.9</td>
<td>7</td>
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<tr>
<td>Anti Prib. Ab</td>
<td>7.7</td>
<td>6.6</td>
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<tr>
<td>T-test</td>
<td>0.27</td>
<td>0.4</td>
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Cognitive T-maze

1st run

2nd run - Choice

<table>
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<tr>
<th>% correct choice</th>
<th>control</th>
<th>APS</th>
<th>anti-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st run</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
swimming test

sec.

day

![Graph showing time in seconds over days.](image)

![Timed test equipment.](image)

![Swimming pool and rat illustration.](image)
CNS-APS Model, Swim Maze
Cognitive T-maze

% correct choice

Day of training

control
APS
anti-P
Linear (control)
Linear (APS)
Linear (anti-P)
Forced swimming test

Anti P rib. Ab injected mice

Control mice

Immobility time (sec)

- control
- APS
- anti-P

- first 120-sec
- last 240-sec
- total 360-sec
Rotarod test

Results of test

<table>
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<tr>
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<th>Time (sec)</th>
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<tr>
<td>Contr</td>
<td>36</td>
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<tr>
<td>Anti P rib. Abs</td>
<td>41</td>
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<tr>
<td>T-test</td>
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</table>

Kazav Aviva PhD
Effect of fluoxetine / anti-ID treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean immobility time (sec)</th>
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<tbody>
<tr>
<td>control (IgG)</td>
<td>60</td>
</tr>
<tr>
<td>anti-P</td>
<td>120</td>
</tr>
<tr>
<td>anti-P + Fluoxetine (L)</td>
<td>80</td>
</tr>
<tr>
<td>anti-P + Fluoxetine (SL)</td>
<td>100</td>
</tr>
<tr>
<td>anti-P + anti-ID IVIG</td>
<td>140</td>
</tr>
</tbody>
</table>

L-Long
Induction of Autoimmune Depression in Mice by Anti–Ribosomal P Antibodies via the Limbic System

Aviva Katzav,1 Inna Solodeev,2 Ori Brodsky,1 Joab Chapman,3 Chaim G. Pick,1 Miri Blank,2 Wei Zhang,4 Morris Reichlin,4 and Yehuda Shoenfeld3

Objective. Autoantibodies against ribosomal P proteins are linked to the neuropsychiatric manifestations of systemic lupus erythematosus (SLE). The present study was undertaken to assess how the specific brain-binding autoantibody anti-ribosomal P can induce a depression-type psychiatric disorder in mice.

Methods. Mice were injected intracerebroventriculally with affinity-purified human anti-ribosomal P antibodies or IgG as control. Pharmacologic and immunologic treatments included the antidepressant drug fluoxetine, the antipsychotic drug haloperidol, and antiidiotypic antibodies. Behavior was assessed by the forced swimming test, motor deficits by rotarod, grip strength, and staircase tests, and cognitive deficits by T-maze alternation and passive avoidance tests.

Results. Anti-ribosomal P antibodies induced depression-like behavior in the mice (mean ± SEM 147.3 ± 19.2 seconds of immobility versus 75.2 ± 12.1 seconds of immobility in IgG-injected control mice; P < 0.005). The anti-ribosomal P antibody–induced depression-like behavior was partially blocked by a specific antiidiotypic antibody and significantly blocked by long-term treatment with fluoxetine, but not by short- or long-term treatment with haloperidol. The depressive behavior was not associated with any motor or cognitive deficits. Anti-ribosomal P antibodies specifically stained neurons in the hippocampus, cingulate cortex, and the primary olfactory piriform cortex, compatible with the previously described binding to the membrane-bound P0 ribosomal protein.

Conclusion. This is the first report of an experimental depression induced by a specific autoantibody. The results implicate olfactory and limbic areas in the pathogenesis of depression in general, and in central nervous system dysfunction in SLE in particular.
Immunohistochemical staining of the mouse brain.

Section No2

Red-violet spots are specific Fast Red staining

anti-P Abs

IVIg-Control

dentate gyrus (DG)

hippocampal fissure (hif)

pyramidal cell layer of the hippocampus

granule cell layer of the dentate gyrus
Selective Involvement of the Amygdala in Systemic Lupus Erythematosus


- The first study to observe damage in the amygdala in patients with SLE.
- Patients with SLE with anti-NMDAR antibodies had more severe damage in the amygdala compared to SLE patients without anti-NMDAR antibodies.
Selective involvement of the Amygdala in Neuropsychiatric SLE

Transversal T1 weighted anatomical MRI scan showing segmentation of the amygdala (purple) and the hippocampus (green)

Bart Emmer et al, (PLoS Medicine 2006;3;2285-2290)
A thinner cerebral cortex and smaller cerebellum were observed in the MRL/lpr substrain. With progression of the disease, the brain area of coronal sections became smaller and the growth of the hippocampus was retarded, which likely contributed to the increase in the ventricle area:brain area ration.

A periventricular pattern of parenchymal damage is consistent with the cerebrospinal fluid neurotoxicity, limbic system pathologic features, and deficits in emotional reactivity previously documented in this model.
A: Binding of anti-Ribos.P to fixed pyramidal cell in rat-hyppocampus cell culture *in-vitro*.

B: penetration of anti-Ribos.P following 4 hrs incubation at 37C.

C: control of A - binding of comercial IgG to fixed rat-hyppocampus cell culture *in-vitro*.

Autoantibodies to Ribosomal P Protein Penetrate into Live cells *Hepatocytes* and Cause Cellular Dysfunction in Culture

Mirna Koscec et al

*JI*, 1997, 159: 2033–2041
Anti-ribosomal phosphoprotein autoantibody triggers interleukin-10 overproduction via phosphatidylinositol 3-kinase-dependant signaling pathways in lipopolysaccharide-activated macrophages

Lee Tp et al

Immunology 2009; 127: 91-102

- High levels of interleukin-10 (IL-10) have been demonstrated to contribute to lupus susceptibility and severity.
- Anti-P mAb promoted IL-10 overproduction in a dose- and time-dependant manner in both lipopolysaccharide (LPS)-activated raw 264.7 cells and primary human macrophages.
- Anti-P mAb enhanced phosphorylation of Akt (PKB; protein kinase B), extracellular signal regulated kinase ½ (ERK1/2) and c-Jun NH2-terminal kinase ½ (JNK1/2), while phosphorylation of p38 remained unaltered.
Peripherally induced anosmia does not cause the same behavioral changes.

A major dysfunction of the cortical-hippocampal-amygdala circuit that underlies the behavioral and other changes.

Chronic, but not acute, administration of antidepressants largely corrects most the behavioral, endocrine, immune and neurotransmitter changes that occur following bulbectomy.
Smell threshold detection test

- Odor: mentha essential oil
- Concentrations (percentage dilution v/v in mineral oil): 0, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100%
- Testing: sniffing and conditioned reflex
Smell threshold

Smell threshold concentration (%)

- control
- APS
- anti-P
Mouse Brain MRI enhanced with Mn sniffing
Differences of MnEMRI signal between “IgG” and “Rib” mice

$P$ (total) = 0.0001
Disturbance in the Sense Smell in Psychiatric Patients

Pryse-Phillips W.

Reduced olfactory performance in patients with major depression


Olfactory detection thresholds (means+S.D.) for eugenol and phenylethylalcohol in MDD patients and healthy controls
Relationship between odor perception and depression in the Japanese elderly

Satoh S, et al.
Aromatherapy

Effect on Treg
Potential antidepressant effects of lemon odor in rats


- Antidepressant effects brought about by olfactory stimulation with various odorants were investigated with the forced swimming test.

- Lemon odor significantly reduced total immobility time and potentiated the imipramine-induced reduction of total immobility time in the test.
Effects of citrus fragrance on immune function and depressive states


- The treatment with citrus fragrance normalized neuroendocrine hormone levels and immune function and was rather more effective than antidepressants.
Lavender fragrance had a beneficial effect on insomnia and depression in women college students.
Improvement of depression with lemon (Forced swimming test -FST)
Olfactory loss in multiple sclerosis


- Odor identification ability.
- 40 patients with definite multiple sclerosis with those obtained in 40 age-, sex- and smoking-habit-matched healthy controls.
- Patients with multiple sclerosis scored significantly poorer than controls on the Cross-Cultural Smell Identification Test (P<0.001).
- Significant correlations between the smell identification score and symptoms of anxiety (r=-0.43, P=0.006), depression (r=-0.42, P=0.008) and severity of neurological impairment (r=-0.32, P=0.05) were found.
Olfactory dysfunction and multiple sclerosis


Administered the Brief Smell Identification Test (BSIT) to 471 older people without dementia or cognitive impairment who then completed annual clinical evaluations and brain autopsy at death.

These analyses suggest that among older people without clinical manifestations of Alzheimer’s disease (AD) or mild cognitive impairment (MCI) olfactory dysfunction is related to both the level of AD pathology in the brain and the risk of subsequently developing prodromal symptoms of the disease.
The aim of this study was to determine the specificity and sensitivity of transcranial sonography (TCS) and the Pocket Smell Test (PST) in differing Parkinson’s disease from essential tremor. Confirming Parkinson’s disease the specificity of TCS was 88.2% and the sensitivity 94.9%. The specificity of PST was 80.4% whereas the sensitivity was 74.6%.

Yehuda Shoenfeld, MD, FRCP, MAACR


I will do anything for grant money.
Smelling a single component of male sweat alters levels of cortisol in women


- We measured salivary levels of the hormone cortisol in women after smelling pure androstadienone (4,16-androstadien-3-one), a molecule present in the sweat of men that has been suggested as a chemosignal in humans.
- Merely smelling androstadienone maintained significantly higher levels of the hormone cortisol in women.
- Like rodents, humans can influence the hormonal balance of conspecifics through chemosignals.
To smell the immune system: Olfaction, autoimmunity and brain involvement

Rael D. Strous, Yehuda Shoenfeld

Autoimmunity Reviews 2006; 6: 54-60
Smell score (TDI) is associated with CNS involvements

CNS involvement was associated with decrease in smell Identification \( (p<0.01) \)
Sniffin' sticks-analysis

SLE patients

TDI score
- TDI<15-functional anosmia
- TDI>30-normosmia
- TDI<30-hyposmia
- 10 SLE and 10 controls

Averages of TDI by top and low SLEDAI

Percentages of TDI
SLE with CNS involvement

SLE with CSF involvement

SLE with CSF involvement

Units

Patient no.
The Sense of Smell in SLE


ARTHРИTIS & RHEUMATISM
1487–1484 60;2009

- In both the SLE and control groups, smell deficit correlated with male sex and older age.

- A decrease in the sense of smell was observed in SLE patients (46%) and controls (25%) ($P < 0.02$), while loss of smell (anosmia) was documented only in SLE patients (10%).

- Total TDI scores and individual stages of smell correlated with SLE Disease Activity Index ($P < 0.001$) and CNS manifestations ($P < 0.03$).

- There is a decrease in smell capability in SLE.
Pregnancy loss and autoimmunity

- Anti-phospholipid syndrome - Criteria
- Systemic lupus erythematosus - Prevalent
- Recurrent pregnancy loss - no defined autoimmune diseases, but presence of multiple ANA antibodies and anti-thyroid antibodies
Olfactory dysfunction and pregnancy loss

- Normosmia (>30): 34 Patients, 10 Controls
- Hyposmia (15-30): 3 Patients, 39 Controls
- Anosmia (<15): 0 Patients, 0 Controls
Olfactory impairment in patients with the fibromyalgia syndrome and systemic sclerosis

Howard Amitai - Nancy Agmon-Levin - Neta Shoenfeld - Yoav Arnon - Daniela Amitai - Pnina Langevitz - Alexandra Babir Gurman - Yehuda Shoenfeld

Published online: 26 November 2014
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Abstract Patients with autoimmune diseases often present with olfactory impairment. The aim of the study was to assess the olfactory functions of female patients with fibromyalgia (FM) compared with patients with systemic sclerosis (SSc) and with healthy female controls. Olfactory functions were assessed in 24 patients with FM, 20 patients with SSc and 21 age-matched healthy controls. The sense of smell was evaluated using the Sniffin’ Sticks test including the three stages of smell threshold, discrimination, and identification (TDI) of the different odors. The severity of fibromyalgia was assessed using the fibromyalgia impact questionnaire (FIQ). The short form 36 (SF-36) questionnaire was also completed in order to seek a relationship between the patients perception of quality of life and the different aspects of the smell sense. Depression was evaluated in both FM and SSc patients utilizing the Beck depression inventory-II (BDI-II) questionnaire. Patients with FM had significantly lower TDI smell scores compared with both SSc patients and healthy controls ($p < 0.005$, One-Way ANOVA). Hyposmia (defined as TDI scores below 30) were observed in 14 of 24 (42%) patients with FM compared to 3 of 20 (15%) patients with SSc and 1 of the healthy controls (4.3%) ($p < 0.02$). FM patients had significantly lower thresholds of smell compared to both healthy controls and patients with SSc ($p < 0.001$), whereas for patients with SSc only the ability to discriminate between odors was impaired ($p < 0.006$). We could not detect any statistical correlation between smell abilities and clinical manifestation of SSc or the FIQ and SF-36 scores among FM patients. However the correlation between depression, defined by the BDI-II score, and the sense of smell differed between patients with FM and patients with SSc. As only among SSc patients a lower sense of smell correlated with a higher BDI-II score ($p = 0.02$). Our findings suggest that there is a decrease in the sense of smell both in FM and SSc patients compared with healthy controls. However these impairments differ between patients group and might represent different mechanisms that affect the sense of smell.

Keywords Olfaction · Smell · Fibromyalgia · Systemic sclerosis · Limbic system

Howard Amitai and Nancy Agmon-Levin have contributed equally to this study.

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Y. Arnon
Division of Cardiology, Meir Medical Center, Kfar Saba, Israel
1. Reduction of olfactory function in idiopathic rapid-eye-movement (REM) sleep behavior disorder (iRBD) is of the same magnitude as that found in patients with Parkinson’s disease (PD) and dementia with Lewy bodies (LBD).

2. The results suggest that OSIT-J, which is a short and simple nonlexical olfactory identification test, can be useful as a clinical indicator for iRBD with Lewy body formation and is appropriate in the Japanese elderly population.

Yehuda Shoenfeld, MD, FRCP.

Watts G, BMJ. 2004; 329: 815

“For their discoveries of odorant receptors and the organization of the olfactory system”.

One receptor recognizes only one type of odorant molecule.

A thousand genes specifying a thousand receptor types are able to distinguish between 10 times as many odours.

Peter Brennan, research fellow in olfaction and behaviour at the University of Cambridge.

“Although this work is not directly related to any major human diseases, it has opened new windows on the way the brain interprets the world around us”.

Richard Axel and Linda B Buck
Cell 65;175-187,1991
Researchers say smells can affect a shopper’s behavior. So stores are trying to cash in on what the nose knows.

ScentAir CEO David Van Epps. “Black cedar adds body, fullness to the aroma. As for the rest of the tones, each has its own characteristics, and it’s as much an art as a science.”

Sony hoped to benefit from both last year when it decided to try to broaden the mix of people shopping for consumer electronics in its U.S. Sony Style stores to include more women. “Our products are about seeing and hearing,” says the stores...
Scents and Sensibility

Researchers say smells can affect a shopper’s behavior. So stores are trying to cash in on what the nose knows

BY JEREMY CAPLAN

The scent calls the odor for the nose. The latest technique for getting in a spending mood is to fill the store with a mix of scents. That’s why Select Comfort, a nationwide U.S. chain of 800 bedding stores, is in the market for one such store. And not just any store, but the world of ScentsAir, one of several firms that design scents for retail settings, has signed a mix of customers: wood, amber, musk, vanilla, jasmine and bergamot. The store would come to a close-up.

The demand for these olfactory products—such as, in a growing body of research that demonstrates how scents can influence human behavior—can be found in Martin Lindstrom’s book "Fragrance," which suggests that although most modern scents are scents, many of the original scents remain on a given customer’s skin. And experiments have shown that even small changes can result in significant differences. For instance, a small change in the scent of a product can affect the way a person perceives the product. And when a product is introduced to a new market, the scent can be adjusted to make it more attractive to the new market.

When Van Eckert met with SonyStyle’s executive team to reveal the short list of scents contenders—carried in small glass vials in his metal lab—she asked each member to give personal preferences and provide feedback. This helped clients avoid having individual quirks, or habits of apples caused by having to eat one every day after school or a mouthful of violets because they called mind being grated on so many things. Cloud the search for a suitable corporate scent. Each scents was limited to just a couple of samples. "This is not a beauty campaign," she says, and one of the benefits of using scents in advertising is that it can be used to make a product more attractive. Toward the end of the process the Sony races had nearly settled on a blend of orange and vanilla, with a hint of cardamom added to the mix. The feminine-leaning smell wouldn’t scare off men. (A male scent had suggested a drop of bourbon, but it was decided that cardamom would provide a similar yet subtler tone.) Then, sitting around a conference table stoned with perfume boxes, the races had a final request: Could the orange be more, more of a blend or an orange? ScentsAir dug into its library of about 400 scents—spices, wood and tangerine—and the tangerine-clad before hitting the jackpot with a robustly bloody red orange.

Not everyone appreciates retailers’ attempts to lead consumers around by the nose. “That might be deliberate and delightful to one person if enough to give the next person a migraine," says Gabrielle Glaser, author of "The Nose: A Profile of Sex, Beauty, and Survival." To Glaser, the idea that Sony would target women with a smell is preposterous. “It’s like Dr. Mommy, we understand you,” she says.

But retailers say the customers prefer it. "We’re not trying to manipulate people," preach Sony’s Belch. "It’s subtle, and it’s mainly about making sure people have a pleasant experience." SonyStyle now uses the scent in each of its 37 U.S. stores.

Other businesses are signing on too, some choosing scents that vary from connections for particular products they want to sell. A technique called "fragrance packaging," Bloomberg’s "The Scent of Success," "the smell of baby powder in an infant clothing department, white fruits of lime and coconut white around the department store's intangible and suds-decorated displays. One of ScentsAir’s most popular scents, fresh-scented chocolate, has been widely used by sellers of model homes, and estate agents in North Carolina to make prospective buyers feel at home the instant they walk in. Upgrade ice cream chains Inzack & Bolle’s recently adopted a waffle cone smell to attract patrons to the shop. And within the Orlando, Florida, Hard Rock Hotel, where sales has been lagging. The effects? Ice cream sales shot up more than a third. To stave off efficiency fatigue—customers typically stop noticing a smell after a minute or two—some retailers use a timed sequence of targeted scents to "decorate" an environment.

Signature scents, like Sony’s or Westin’s, run at $5,000 to $25,000, depending on how complicated they are to design. Companies also pay monthly subscription fees to rent fan machines that disperse the scents into the air. Smaller retailers can buy simple smells—such as a single scent to enhance a specific fragrance. ScentsAir even offers a line of essential oil scents, one to five scents per bottle in an "aroma-eucalyptus, white grapefruit, lemon, rosemary, and lavender."
“……using your genetic sequence as the blueprint to create your exclusive elixir…..”

www.mydnafragrance.com/perfume.   My DNA Fragrance, Beverly Hills, CA, USA
Everything *is* autoimmune until proven otherwise.
Even psychiatric conditions
Thank you
Five Jews change the way we see the world:

Moses: “the Law is everything.”

Jesus: “Love is everything.”

Marx: “Money is everything.”

Freud: “Sex is everything.”

Einstein: “Everything is relative.”
Decreased smell was observed in patients with SLE.

Additional studies

- Olfactory dysfunction and pemphigus, vasculitis and anti-phospholipid syndrome.
- Olfactory dysfunction and scleroderma.
- Olfactory dysfunction and fibromyalgia.
Conclusions

Sense of smell

Olfactory dysfunctions

The immune system

Autoimmune diseases
A total of 1,375 participants aged 60 years or older had their olfaction measured using the San Diego Odor Identification Test. Quality of life was assessed using the 36-Item Short-Form Survey (SF-36). Depressive symptoms were assessed by either the SF-36, which included the Mental Health Index, and/or the Center for Epidemiologic Studies Depression Scale (CES-D-10).

Among participants with olfactory impairment, 15.4% and 20.2% had depressive symptoms assessed by the Mental Health Index and CES-D-10, respectively. Among participants aged 70 years or older, olfactory impairment was associated with depressive symptoms (assessed by the CES-D-10).
Association of hippocampal atrophy with cerebrospinal fluid antibodies against the NR2 subtype of the N-ethyl-D-aspartate receptor in patients with systemic lupus erythematosus and patients with primary Sjogren’s syndrome


J Rheumatol 2015

- Fifty patients with SLE and 50 patients with primary SS underwent clinical examination and cerebral magnetic resonance imaging.
- Anti-NR2 antibodies in cerebrospinal fluid (CSF) were measured, and hippocampal gray matter volumes were compared between patients who were positive for and those who were negative for anti-NR2 antibodies.
- Patients with anti-NR2 antibodies in CSF had less hippocampal gray matter than patients without these antibodies.
- Anti-NR2 antibodies in patients with SLE and primary SS cause neuronal death manifested as reduced hippocampal gray matter, as has been previously demonstrated in mice with autoimmune disease.
NMDA Receptor

Epinephrine + DWEYS
(Kowal et al., Immunity, 2004)

LPS + DWEYS
(Huerta et al., Proc Natl Acad Sci USA, 2006)

Anti-DNA
A 10-item smell identification scale related to risk for Alzheimer’s disease

Tabert MH et al
Ann Neurol 2005; 58:155-60

Strongly predicted conversion to Alzheimer’s disease on follow-up evaluation in patients with mild cognitive impairment.
Complement involvement in depression induced by anti P ribosomal IgG and aC5a.
Human anti-Ribosomal P and neuronal marker MAP2 on differentiated human neuronal cells
Animal models of depression: olfactory lesions affect amygdala, subventricular zone, and aggression.


- Analyze the behavioral symptoms and neuroanatomical correlates after mucosal damage or ablation of the olfactory bulb.