Olfaction in Neurodegenerative Diseases

Richard L. Doty, Ph.D.
Director
Smell and Taste Center
University of Pennsylvania Medical Center
Philadelphia, PA 19104
www.med.upenn.edu/stc

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Disclosure: Dr. Doty is a major shareholder in Sensonics, Inc., the manufacturer and distributor of smell and taste tests.

“Smell” in The Lady & the Unicorn Tapestries, c. 1500, Musee de Cluny, Paris
OLFACTION: THE NEGLECTED SENSE
TWO MAJOR MISCONCEPTIONS IN NEUROLOGY

- Olfaction is not important
- There are 12 cranial nerves
OLFACTION IS IMPORTANT TO THE PATIENT

- Flavor and Palatability of Foods and Beverages
- Aesthetics (perfumes, flowers, enjoyment)
- Safety (warning of spoiled foods, poisons, toxins, polluted air, smoke/fire, leaking gas)
- Basic Body Functions (ingestion, digestion, cephalic reflexes, sexual behavior, memory)
- Elements of communication (Mother/infant interactions, personal identification, hygiene)
- Occupational tool (e.g., cooks, firefighters, plumbers, wine merchants, food and drug specialists, chemical plant workers, policemen, etc.)

- Olfactory loss can be an early sign of serious diseases, including Alzheimer’s Disease, Parkinson’s Disease, multiple sclerosis, tumors, epilepsy, endocrine disturbances, and malnutrition

- Olfaction is first and foremost a hedonic sense, providing pleasure and displeasure, as demonstrated by the next three slides.
THE GOOD
THE BAD
WHY SHOULD THE PSYCHOLOGIST OR NEUROLOGIST QUANTIFY OLFACTORY FUNCTION?

- Monitor disease progression & determine treatment efficacy and prognosis
- Provide objective information regarding workman’s compensation and other insurance or legal claims
- Detect early signs of tumors and neurological disorders that may not be discerned otherwise and to maximize efficacy of intervention or treatment
- Detect malingering
- Communicate accurate information to patients regarding the level of dysfunction and whether it is normal for their age and sex, as patient subjective reports can be misleading
**Major Point:**

The majority of chemosensory complaints are a result of smell disturbance only.

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HOW IS OLFACIOn MEASURED?
ASSESSING SMELL FUNCTION

Psychophysical Tests
- Odor Identification
- Odor Detection
- Odor Discrimination/ Memory

Electrophysiological Tests
- Electro-olfactogram
- Event-Related Potential

Psychophysiological Tests
- Cardiovascular Changes
- Inhalation Changes

Structural & Functional Imaging
- Magnetic Resonance Imaging (MRI) & functional MRI (fMRI)
- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT)
- Diffusion Weighted Imaging (DWI)
## Published Clinical Olfactory Tests

*(modified from Doty, *Amer. J. Rhinology*, 2007, 21, 460-473.)*

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Published by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta Smell Test (Green &amp; Iverson, 1998)</td>
<td>Odor Memory Test™ (Choudhury et al., 2003)</td>
</tr>
<tr>
<td>Alcohol Sniff Test (Davidson &amp; Murphy, 1997).</td>
<td>Odor Stick ID Test (Saito et al., 2006)</td>
</tr>
<tr>
<td>Amoore threshold test (Amoore &amp; Ollman, 1983)</td>
<td>Pocket Smell Test™ (PST) (Solomon et al., 1998)</td>
</tr>
<tr>
<td>Barcelona Smell Test-24 (Cardesin et al., 2006)</td>
<td>Quick Smell ID Test™ (Q-SIT) (Jackman &amp; Doty, 1999)</td>
</tr>
<tr>
<td>Biolfa® olfactory test (Bonfils et al., 2004)</td>
<td>San Diego Odor ID Test (Anderson et al., 1992)</td>
</tr>
<tr>
<td>B-SIT (aka Cross-Cultural SIT) (Doty et al., 1996)</td>
<td>Scandinavian Odor ID Test (Nordin et al., 1999)</td>
</tr>
<tr>
<td>CCCRC Test (Cain et al., 1983)</td>
<td>Smell Diskettes (Simmen et al., 1999)</td>
</tr>
<tr>
<td>Combined Olfactory Test (Lam et al., 2006)</td>
<td>Smell Threshold Test™ (Doty, 2000)</td>
</tr>
<tr>
<td>Dutch Odour Identification Test (Hendriks, 1988)</td>
<td>Sniff Magnitude Test (Frank et al., 2003)</td>
</tr>
<tr>
<td>ETOC (Thomas-Danguin et al., 2003)</td>
<td>Sniff ‘n Sticks Test (Kobal et al., 1996)</td>
</tr>
<tr>
<td>Jet Stream Olfactometer (Ikeda et al., 1999)</td>
<td>Toyota &amp; Takagi (T&amp;T) Olfactometer (Takagi, 1989)</td>
</tr>
<tr>
<td>Kremer Olfactory Test (Kremer et al., 1998)</td>
<td>T&amp;T with computer sequences (Eloit &amp; Trotier, 1994)</td>
</tr>
<tr>
<td>Le Nez du Vin (McMahon &amp; Scadding, 1996)</td>
<td>UPSIT (Doty et al., 1984)</td>
</tr>
<tr>
<td>Odor Confusion Matrix (Wright, 1987)</td>
<td>Viennese Odor Test (Lehrner &amp; Deecke, 1999)</td>
</tr>
</tbody>
</table>
University of Pennsylvania Smell Identification Test (UPSIT)

- Self-administered in 15 min.
- 40-items
- Test-retest reliability = 0.94
- Forced-choice
- Norms based upon ~ 4,000 persons
- Categorization of dysfunction into mild, moderate, severe and total categories
- Percentile Ranks for 5-year age categories
- Detects malingering
- Available commercially in multiple languages as the Smell Identification Test™ or SIT
- Hundreds of medical publications based on this test (see academic publications at www.sensonics.com)

Photo courtesy of Sensonics, Inc., Haddon Heights, NJ (www.smelltest.com)
UPSIT Normative Data
Detecting Malingering

WHAT ARE THE CAUSES OF CN I DYSFUNCTION?

- Acquired immune deficiency syndrome (AIDS)
- Adenoid hypertrophy
- Age
- Alzheimer’s disease
- Amyotrophic lateral sclerosis
- Anorexia nervosa
- Asperger’s syndrome
- Attention deficit/hyper-reactivity disorder
- Bardet-Biedl syndrome
- Chronic alcoholism
- Cystic fibrosis
- Degenerative ataxias
- Diabetes
- Down syndrome
- Epilepsy
- Head trauma
- Hypothyroidism
- Huntington’s disease
- Iatrogenesis
- Kallmann syndrome
- Korsakoff psychosis
- Medications (e.g., antimicrobials, antilipid agents, antihypertensives)
- Multi-infarct dementia
- Neoplasms, Cranial/Nasal
- Multiple sclerosis
- Nutritional deficiencies
- Obstructive pulmonary disease
- Parkinson’s disease
- Parkinson’s dementia complex of Guam
- Pick’s disease
- Pseudohypoparathyroidism
- Restless leg syndrome
- Rhinosinusitis/Polyposis
- Schizophrenia
- Stroke
- Tobacco smoking
- Toxic chemical exposure
- Upper Respiratory Infections
- Usher syndrome

*Highest frequency of clinical presentation to a smell & taste center*
PARKINSON’S DISEASE
The Sensory Signs of PD were Incorrectly Characterized by James Parkinson in 1817

James Parkinson defined the disorder that now carries his name in *An Essay on the Shaking Palsy* as follows:

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellect being uninjured.”

What if PD patients were visually impaired or blind instead of hyposmic or anosmic? And the blindness came first? This disease would probably be classified as a visual disorder with motor accompaniments.
CHARACTERISTICS OF PD-RELATED OLFACTORY DYSFUNCTION

- Present in ~ 90% of PD patients
- More prevalent than tremor
- Found in both familial and non-familial cases
- Rarely total (i.e., anosmia is not the norm)
- Detectable by wide range of olfactory tests
- Typically bilateral; any L:R variation unrelated to side of hemiparkinsonism
- Unrelated to disease stage, motoric, or other signs of PD, although correlated in early PD with SPECT imaging of striatal dopamine transporter uptake
- Indistinguishable in terms of frequency or magnitude from that of AD and Parkinson-dementia complex of Guam
- Unresponsive to anti-PD medications
- Present in some asymptomatic relatives who exhibit dopamine transporter deficits and who eventually develop clinically defined PD
- Likely present 2-4 years before onset of motor symptoms
40+ Psychophysical Studies of Olfactory Dysfunction in PD

- Anasari and Johnson, 1975: Detection threshold
  D (0.05)
- Ward et al., 1983: Odor detection, thresh, discrim
  D (0.01, 0.03, nst)
- Corwin and Serby, 1985: Yes/No ID with UPSIT odors
  D (nst)
- Serby et al., 1985: Yes/No ID with UPSIT odors
  D (0.05)
- Quinn et al., 1987: Detection threshold
  D (0.001)
- Doty et al., 1988: UPSIT, detection threshold
  D (0.0001, 0.0001)
- Kesslak et al., 1988: UPSIT, odor matching task
  D (0.05, nst)
- Doty et al., 1989: UPSIT
  D (0.0001)
- Murofushi et al., 1991: Detection thresh, recogn thresh
  D (0.01, 0.05)
- Doty et al., 1991: UPSIT
  D (0.001)
- Hawkes and Shepard, 1993: UPSIT
  D (0.001)
- Stern et al., 1994: UPSIT
  D (0.001)
- Doty et al., 1995: UPSIT
  D (0.001)
- Lehrner et al., 1995: Detection thresh, ID, memory
  D (nr)
- Wenning et al., 1995: UPSIT
  D (0.001)
- Barz et al., 1997: Odor driscrim, ID, OERP
  D (ns, 0.001, 0.05)
- Hawkes et al., 1997: UPSIT, OERP
  D (0.0001, 0.001)
- Ahlskog et al., 1998: UPSIT – Modified
  D (0.01)
- Hawkes and Shepard, 1998: UPSIT, OERP
  D (0.0001, nst)

nst, no statistical test applied; nr, not reported; D, decreased performance in values relative to age-matched controls; UPSIT, University of Pennsylvania Smell Identification Test; ID, Odor identification test; OERP, olfactory event-related potentials; SS, Sniffin’ Sticks; B-SIT, brief smell identification test.
<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daum et al., 2000</td>
<td>SS, Detection threshold</td>
<td>D (0.001, 0.001)</td>
</tr>
<tr>
<td>Montgomery et al., 2000a</td>
<td>UPSIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Montgomery et al., 2000b</td>
<td>UPSIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Tissingh et al., 2001</td>
<td>B-SIT, detection &amp; discrimination</td>
<td>D (0.001, 0.001, 0.001)</td>
</tr>
<tr>
<td>Zucco et al., 2002</td>
<td>ID, Odor Matching</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Müllner et al., 2002</td>
<td>SS</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Sobel et al., 2002</td>
<td>UPSIT, detection threshold 2 odors</td>
<td>D (0.0001, 0.007*, 0.003**)</td>
</tr>
<tr>
<td>Double et al., 2003</td>
<td>B-SIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Hudry et al., 2003</td>
<td>ID &amp; multiple trait ratings</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Katzenschlager et al., 2004</td>
<td>UPSIT</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Khan et al., 2004</td>
<td>UPSIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Sommer et al., 2004</td>
<td>SS</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Ondo &amp; Lai, 2005</td>
<td>UPSIT</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Marras et al., 2005</td>
<td>UPSIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Siderowf et al., 2005</td>
<td>UPSIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Bohnen et al., 2007</td>
<td>UPSIT</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Ferreira et al., 2007</td>
<td>UPSIT</td>
<td>D (0.0001)</td>
</tr>
<tr>
<td>Kim et al., 2007</td>
<td>B-SIT</td>
<td>D (0.001)</td>
</tr>
<tr>
<td>Lee et al., 2007 (2 studies)</td>
<td>B-SIT</td>
<td>D (0.001, 0.001)</td>
</tr>
<tr>
<td>Quaglìato et al., 2007</td>
<td>B-SIT</td>
<td>D (0.0001)</td>
</tr>
</tbody>
</table>

**ns**, no statistical test applied; **nr**, not reported; **D**, decreased performance in values relative to age-matched controls; **UPSIT**, University of Pennsylvania Smell Identification Test; **ID**, Odor identification test; **OERP**, olfactory event-related potentials; **SS**, Sniffin’ Sticks; **B-SIT**, brief smell identification test; * vanillin; ** proprionic acid.
UPSIT and Threshold Test Scores Significantly Altered in PD

# Olfactory Testing: Sensitivity & Specificity in Discriminating PD Patients from Normals

Doty et al., *Neurodegeneration*, 2005, 4, 93-97

<table>
<thead>
<tr>
<th>Age Group</th>
<th>UPSIT Cut-Off</th>
<th>Men</th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>≤ 60 yrs</td>
<td>31 M 33 W</td>
<td>0.91</td>
<td>0.88</td>
<td>0.79</td>
<td>0.85</td>
</tr>
<tr>
<td>61-70 yrs</td>
<td>25 M 30 W</td>
<td>0.81</td>
<td>0.82</td>
<td>0.80</td>
<td>0.88</td>
</tr>
<tr>
<td>≥ 71 yrs</td>
<td>22 M 25 W</td>
<td>0.76</td>
<td>0.78</td>
<td>0.78</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Respective sample sizes for the PD & normal subject groups: ≤ 60 yrs: males, 32 & 128; females, 28 & 112; 61-70 yrs: males, 52 & 76; females, 20 & 104; ≥ 71 yrs: males, 25 & 100; females, 23 & 92.
Hyposmic Relatives More Likely to Develop PD than Normosmic Relatives

- 361 asymptomatic relatives of PD patients administered tests of odor identification, detection & discrimination
- Nigrostriatal dopamine function assessed using SPECT with $^[123]I\beta$-CIT dopamine transporter ligand assessed in 40 hyposmic and 38 normosmic relatives
- The only relatives who developed PD during a 2-year follow-up period were from the hyposmic group (4/40 or 10%)
- Increased rate of decline in $^[123]I\beta$-CIT dopamine transporter binding present in these 4 and another 5 hyposmic relatives
- Conclusion: Risk of developing PD in presence of hyposmia may be as high as 22%
[\textsuperscript{99m}Tc]TRODAT-1 SPECT imaging correlates with UPSIT scores in early Parkinson’s disease


- 24 PD patients (mean age = 58.7 yrs; 20 unmedicated) with mild PD-related symptoms administered the UPSIT
- Nigrostriatal dopamine function assessed using SPECT with [\textsuperscript{99m}Tc] TRODAT-1 dopamine transporter ligand
- A strong and consistent relationship was found between UPSIT scores and dopamine transporter binding in the putamen
- Disease duration or ratings of motor severity did not correlate with either TRODAT binding or UPSIT scores
- Conclusion: Olfactory testing may be a useful biomarker for changes within the dopamine motor system early in the course of PD
Striatal $[^{99}\text{Tc}]$ TRODAT Uptake for the Caudate and Putamen
Partial correlations between UPSIT, motor scores, symptom duration, and age with specific uptake values (SUVs) for striatal regions of interest

<table>
<thead>
<tr>
<th></th>
<th>Caudate</th>
<th>Putamen</th>
<th>Whole Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPSIT</strong></td>
<td>0.36</td>
<td>0.74*</td>
<td>0.66**</td>
</tr>
<tr>
<td><strong>UPDRS (motor)</strong></td>
<td>-0.12</td>
<td>-0.23</td>
<td>-0.20</td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td>0.09</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Age in Yr</strong></td>
<td>-0.12</td>
<td>0.29</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*P < 0.01; **P < 0.001; P > 0.15 for all others
Siderowf et al., Cont.

Relationship between UPSIT scores and [$^{99m}$Tc]TRODAT-1 SPECT specific binding for the whole putamen (p < 0.001)
WHAT IS THE BASIS FOR THE SMELL LOSS OF PARKINSON’S DISEASE?
Three Hypotheses

- Susceptibility of olfactory structures to early disease propagation (Olfactory Vulnerability Hypothesis)

- Olfactory system damage from uptake of pathogen associated with disease induction (Olfactory Vector Hypothesis: Brain Invasion)

- Olfactory system damage from any cause (e.g., head trauma, viruses) induces neurodegenerative disease in genetically susceptible individuals (Olfactory Damage Hypothesis)

These hypotheses are not necessarily mutually exclusive
Olfactory dysfunction is a component of the disease process, reflecting the vulnerability of the olfactory system to disease-related damage.
POTENTIAL REASONS FOR OLFACTORY SYSTEM VULNERABILITY

- Olfactory receptor cell neurons are unmyelinated
- Second order neurons are sparsely myelinated
- Metabolism is high in neurons undergoing regular degeneration/ regeneration, increasing vulnerability to oxidative stress
- Biochemical predisposition to disease pathology, with intrinsic risk factors for such predisposition
OLFACTORIO VECTOR
HYPOTHESIS: BRAIN INVASION

Olfactory dysfunction results, directly or indirectly, from damage to the olfactory pathways as a result of an environmental virus, toxin, or other xenobiotic agent passing from the nasal cavity into the brain via the olfactory nerves.
Anatomy of olfactory mucosa well suited for brain invasion of xenobiotics

- Ciliary surface of olfactory neuroepithelium exceeds 23 cm², providing large region for xenobiotic penetration or receptor incorporation.
- Receptor cell is first order neuron with no synapse between nasal cavity and brain.
- Receptor cells not protected by blood brain barrier.
- Active intracellular transport of viruses and metals well established.
- Perineural spaces allow transport of some xenobiotics from mucosa to subarachnoid space.
History Highlights of Nose Brain Linkage

**Galen (AD 130-200):** Noted permeability of the dura around the cribiform plate to both water and air; believed organ for smell was within the ventricles

**Schwalbe (1869):** Demonstrated that dyes injected into subarachnoid space traveled to nasal mucosa and then to cervical lymph nodes

**Flexner (1910):** Presented evidence that polio virus enters the simian brain via the olfactory mucosa

**Goodpasture (1925):** Showed Herpes simplex virus transported within nerves

**Olitsky & Cox (1934):** Tannic acid solution infused into nose prevented intranasal equine encephalomyelitis virus infection in mice.

**Brodie, Schultz & Gebhardt (1934):** Cutting or cauterizing simian olfactory nerve blocked development of polio after intranasal viral introduction

**Armstrong & Harrison (1935):** Demonstrated protection against intranasal inoculations of polio virus by alum and picric acid douching of nose

**Armstrong (1936):** Alabama field trial to prevent polio in humans with picric acid spray

**Tisdall et al. (1937):** Spraying of 4,713 school children of Toronto with zinc sulfate as polio prophylaxis
Brain Invasion – Defense Mechanisms to Prevent Access of Extrinsic Substances into the CNS through the Olfactory System

- Intracellular detoxification of molecules (P-450)
- Removal of substances by ligand-specific binding proteins (odorant binding proteins)
- Cellular immune responses
- Degeneration and replacement of damaged receptor neurons with new basal stem cell-derived cells
- Olfactory bulb-specific defenses (IL-12)
Observations in Accord with the Olfactory Vector Hypothesis

- Early and seemingly non-progressive olfactory loss in PD could reflect damage from a xenobiotic.

- Many xenobiotics linked epidemiologically to PD can enter olfactory receptor cells (e.g., pesticides, viruses, ionized metals) and are known to be toxic to these cells.

- The proneurotoxin, MPTP, when intravenously injected by humans, largely spares olfaction but when administered intranasally to rats alters olfaction and induces progressive impairments in olfactory, cognitive and motor function in a sequence similar to that proposed by Braak and colleagues.

- A mutation in the P450 cytochrome CYP2D6-desbrisoquinine hydroxylase gene, which would be expected to alter protective mechanisms within the olfactory mucosa, increases the risk of developing PD.
Stage 1: Lewy bodies (LB) form within the olfactory bulb and dorsal motor nucleus of the vagal nerve.

Stages 2 & 3: LB pathology expands into additional brain stem nuclei (e.g., locus coeruleus and substantia nigra) and then into the amygdala.

In Stages 4 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6 when the pathology involves significant regions of the substantia nigra and related brain areas.

PD-related Lewy Body Pathology Appears to Evolves in Predictable Stages (Braak et al).
### Examples of metals capable of incorporation into olfactory receptor cells from the nasal cavity and transported to other brain regions


<table>
<thead>
<tr>
<th>Metal</th>
<th>Species</th>
<th>Method of Application</th>
<th>Receptor Cell Incorporation</th>
<th>Trans-neuronal Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum lactate</td>
<td>Rabbit</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Indirect Evidence</td>
</tr>
<tr>
<td>Aluminum silicate</td>
<td>Rabbit</td>
<td>Bedding</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Aluminum acetyl acetonate</td>
<td>Rat</td>
<td>Inhalation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Rat &amp; Pike</td>
<td>Intranasal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadmium chloride</td>
<td>Rat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadmium oxide</td>
<td>Rat</td>
<td>Aerosol</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Cobalt</td>
<td>Rat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Salmon</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Gold</td>
<td>Squirrel Monkey</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Rabbit</td>
<td>Mucosal</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Iron Oxide (Fe$_2$O$_3$)</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Manganese</td>
<td>Rat &amp; Pike</td>
<td>Intranasal</td>
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<td>Yes</td>
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<tr>
<td>Mercury</td>
<td>Rat &amp; Pike</td>
<td>Intranasal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nickel</td>
<td>Rat &amp; Pike</td>
<td>Intranasal</td>
<td>Yes</td>
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<tr>
<td>Zinc</td>
<td>Rat &amp; Pike</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
### Examples of viruses capable of incorporation into olfactory receptor cells from the nasal cavity and transported to other brain regions


<table>
<thead>
<tr>
<th>Virus</th>
<th>Species</th>
<th>Method of Application</th>
<th>Receptor Cell Incorporation</th>
<th>Trans-neuronal Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno (recombinant)</td>
<td>Rat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aujeszky’s disease (Pseudorabies)</td>
<td>Pig</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Borna disease</td>
<td>Rat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bovine herpes</td>
<td>Goat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Probable</td>
</tr>
<tr>
<td>Canine distemper</td>
<td>Ferret</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ectromelia</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Equine herpes</td>
<td>Pig</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Rat &amp; Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza A</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Primate &amp; Rat</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rabies</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Hamster</td>
<td>Interperitoneal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sendai</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Semliki forest</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
<td>Age-dependent</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis virus</td>
<td>Mouse</td>
<td>Subcutaneous</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vesicular stomatitis virus</td>
<td>Mouse</td>
<td>Intranasal</td>
<td>Yes</td>
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</tbody>
</table>
Inoculated HSV-1 and MHV into bulb. Control mice inoculated into ventricles.

Each virus spread to infect a unique And only partially overlapping set of connections of the main olfactory bulb.

Only HSV infected noradrenergic neurons of the locus coeruleus, while both viruses infected dopaminergic neurons of the ventral tegmental area

**MHV**
- basal forebrain
- hypothalamus
- subthalamic nucleus
- pons
- medulla

**HSV-1**
- hippocampus
- amygdala
- insular regions (temporal lobes)
Observations in Disaccord with the Olfactory Vector Hypothesis

- Existence of genetic and familial forms of PD
- Lack of smell dysfunction in some PD patients
- No direct evidence of pathogen invasion
- Early pathological involvement of non-olfactory brain regions in addition to olfactory brain regions; i.e., the dorsal motor nucleus of the vagus nerve
This hypothesis does not preclude other causes of PD
The mode of entry of pathogens into the brain need not be viewed as exclusive from genetic determinants & epigenetic processes cannot be excluded
The dorsal motor nucleus has close associations with the olfactory pathway
A pathogen could enter the brain via both the olfactory and the vagus nerve, e.g., by entering the nose and being swallowed with the nasal secretions, passing the stomach wall into the vagus nerve, as hypothesized recently by Hawkes et al.
OLFACTORY DAMAGE HYPOTHESIS

Olfactory system damage from any cause (e.g., head trauma, viruses, toxic agents, drug abuse) induces neurodegenerative disease in genetically susceptible individuals; in other words, the damage to the olfactory system need not be due to a xenobiotic associated with disease induction.
Observations in Accord with the Olfactory Damage Hypothesis

- Olfactory dysfunction precedes disease development
- Major risk factors for PD also damage the olfactory system (e.g., age, head trauma, viruses, ionized metals, pesticides)
- Olfactory bulbectomy in rodents produces degeneration within regions of the temporal cortex, hippocampus, and raphe nucleus
- Olfactory bulbectomy induces abnormal protein accumulations, e.g., β-amyloid, in brain regions receiving olfactory bulb projections
- Damage to the human olfactory mucosa induces significant volume decrements in the olfactory bulb and tracts, and may possibly induce neural changes in higher brain regions.
CONCLUSIONS

The olfactory system is intimately associated with Parkinson’s disease.

The nature of this association is poorly understood.

The smell loss could reflect (a) the disease process, per se, (b) an environmental agent that enters the brain to induce the disease process, (c) damage from any of a number of causes that induce PD in genetically susceptible individuals, or (d) combinations of the above.
Thank you for your attention

Smell you around!!!