Fondazione G. Monasterio
CNR - Regione Toscana, Pisa
Italy

Functional Magnetic Resonance Imaging (fMRI)
of the Olfactory System

Domenico Montanaro
INTRODUCTION
The sense of smell is among the most primitive of senses from an evolutionary point of view.

Well developed in animals: fundamental modality for interacting with the environment: Identification of food enhancing pleasure and warning against impending danger.

But it is the least understood of the human senses and limited for:

- less development in humans;
- very subjective expression;
- the lack of an appropriate animal model;
- eliciting memories and emotions.
Olfactory capabilities are typically associated with **macrosomatic mammals**

D. Montanaro, D. De Marchi, S. Burchielli.
A multi-modal approach to the **rabbit brain**: MRI, MRI-DTI, CT-PET and Neuropathology.
Internal Data: working in progress. 2009-2011
Human sense of smell too is extraordinary

**IDENTIFICATION:** human mothers can identify their babies by smell (Porter et al., 1983), and human babies can identify the smell of their breast-feeding mothers by 6 days after Birth.

**DETECTION:** the odorant ethyl mercaptan, often added as a warning sign to propane: detectable by human nose at concentrations far below 1 part per billion ppb (Whisman et al., 1978): it is possible to distinguish between two Olympic sized swimming pool, that containing just three drops of odorant.

HUMAN IDENTIFICATION
Odors with appropriate linguistic labels

**Limitation**: need alternative to choose from, naming even common odors with a success rates 50%

Odor **familiarity** can improve subjects ability to identify odors

No difficulty in applying general **descriptors** related to odorant characteristics. The primary perceptual aspect of odorants is **valence** (pleasantness)
Methods of choice for olfactory evaluation

OERP could not be present in some normosmic subjects

OERP not detectable in 80% of the subjects with diagnosed functional anosmia.

The presence of OERP is compatible with the diagnosis of “functional anosmia” but not with complete anosmia.

Jorn Lotsch, Thomas Hummel
The clinical significance of electrophysiological measures of olfactory function
Methods of choice for olfactory evaluation

• X-ray computed tomography (x-CT) and MRI: For assessment of the peripheral causes of olfactory deficits only.

• Brain perfusion single photon emission tomographic (SPECT) imaging: to identify the areas involved in odor identification.

• advanced functional neuroimaging techniques: Positron Emission Tomography (PET) and functional MRI (fMRI).
LIMITS

**PET**: the anatomic location of major olfactory structures at the base of the brain makes PET scanning inaccurate and difficult to quantify;

**fMRI**: presence of air sinuses near the base of the brain, where the relevant anatomical structures are located.
Susceptibility artifacts

3T MRI
Artifact correction: mouth insert diamagnetic passive shim
Ease while wearing the intraoral shims
Odor stimulating apparatuses

Olfactometer (*Olfactoforus*)

Conditioned in fMRI than PET due to magnetic fields

- Pieces of magnetic metal can be *attracted* into the magnet: potential risk for the physical and subject integrity;
- Materials including magnetic pieces and/or producing electromagnetic wave radiation can *modify field lines* and induce image distortion.
A stimulation method using odors suitable for PET and fMRI studies with recording of physiological and behavioral signals

Journal of Neuroscience Methods 142 (2005) 35–44
F. Frijia … D. Montanaro
IEEE, Vigo Jun 2007
Time course

With chemical senses the perception time-course might be rather unpredictable from the stimulation paradigm.

... “Data processing algorithms which are satisfactory with other sensory studies such as vision or audition, may drastically fail to detect activation with chemical senses: the response may build up very slowly, taking several seconds to reach its maximum” ...

Different statistical approaches for modeling time course

Pierre-Francois .... Denis Le Bihan
Latencies in fMRI Time-Series: Effect of Slice Acquisition Order and Perception
Matthias H. Tabert et AL.
Validation and optimization of statistical approaches for modeling odorant-induced fMRI signal changes in olfactory-related brain areas
Neurolmage 34 (2007) 1375–1390
Noam Sobel et Al.
Blind smell: brain activation induced by an undetected air-borne chemical
Brain (1999), 122, 209–217
F. Frijia ... D. Montanaro
IEEE, Jun 2007
Federico Vanni ... Domenico Montanaro

Functional Magnetic Resonance Imaging (fMRI) of the Human Olfactory System: Stimulation and Statistical Data Analysis in Normosmic and Congenital Anosmic Subjects

XII OHBM, 2006.
Individual results may not completely duplicate group analysis findings and provides additional information about localization and lateralization of activations
The occurrence of each activated area was estimated as *percentage* with respect to the number of runs in which the same molecule was administered.

Analysis of significant differences *p-statistic* with binary logistic regression.
### Individual Analysis

<table>
<thead>
<tr>
<th>P values &lt;</th>
<th>10-20 vs Random</th>
<th>HH vs Menthol separately</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HH</td>
<td>Menthol</td>
</tr>
<tr>
<td>Cerebellum R</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cerebellum L</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Piriform Cortex R</td>
<td>0,007*</td>
<td>ns</td>
</tr>
<tr>
<td>Piriform Cortex L</td>
<td>0,033*</td>
<td>ns</td>
</tr>
<tr>
<td>Orbito-Frontal C. R</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Orbito-Frontal C. L</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Insula R</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Insula L</td>
<td>0,064*</td>
<td>ns</td>
</tr>
<tr>
<td>Cingulum R</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cingulum L</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Parietal R</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Parietal L</td>
<td>ns</td>
<td>0,059*</td>
</tr>
</tbody>
</table>

* = more 10-20

* = more HH
° = more M

Domenico Montanaro et Al.
Functional MRI (fMRI) of olfactory system: persistence of brain activation to odors in Kallmann Syndrome
XXXII ESNR, Genova, 20-23 Settembre 2007

F. Frijia, D. Montanaro et Al.
XIII OHBM, Chicago Jun 2007
Olfactory cortical organization vs Other distal senses

1. Direct projection from second-order sensory neurons to cortex, without a thalamic relay

2. Extent of connections from cortex back to the earlier processing levels, mainly the olfactory bulb
Nobel Lectures

Unraveling the Sense of Smell (Nobel Lecture)**
Linda B. Buck*

Scents and Sensibility: A Molecular Logic of Olfactory Perception (Nobel Lecture)**
Richard Axel*
Zelano C et Al.
Attentional modulation in human primary olfactory cortex
Primary olfactory (piriform) cortex

- Synthetic experience-dependent coding of odor quality.
- Repository of olfactory memory traces.
- Dissociation: Temporal subregion, non attentional responses; Frontal subregion, attentional sniffs.

Zelano C et Al.
Attentional modulation in human primary olfactory cortex
The spatial source of an odorant is determined by comparing input across nostrils.

Nostril-specific responses are located in POC for left versus right localization. It is engaged also portion of the superior temporal gyrus: similar to visual and auditory localization.

System for spatial representation of multisensory inputs.

Posterior piriform cortex
Irrespective of underlying molecular composition, odors are encoded as odor-object categories akin to visual object forms in human ventral temporal cortex.

Semantic associations, sensory context, and perceptual learning Via re-entrant influences from centres as OFC and hippocampus

Sub serve a role otherwise provided by the thalamus
detection, analysis, and transformation of a sensory signal

Jay A. Gottfried ... Raymond J. Dolan
Dissociable Codes of Odor Quality and Odorant Structure in Human Piriform Cortex
Neuron 49, 467–479, February 2, 2006
Odorant-induced fMRI activation in POC is weak

Specific technical homogeneity of fMRI signal in the ventral temporal region

Odorants induce a sharp increase in POC activation, which then rapidly habituates despite continued odorant presentation and detection

Noam Sobel …… And John D. E. Gabrieli
Time Course of Odorant-Induced Activation in the Human Primary Olfactory Cortex
Habituation or Desensitization Effects

Limiting factors for visualizing olfactory activation in the primary olfactory cortex.

Adaptation of the olfactory receptor neuron or the habituation of the primary olfactory cortex.
Alexander Poellinger et al.
Activation and Habituation in Olfaction—An fMRI Study
NeuroImage 13, 547–560 (2001)
Amygdala and Entorhinal Cortex

The anterior cortical nucleus of the amygdala and the periamygdaloid cortex receive direct projections from and project information back to the olfactory bulbs.

Christina Zelano and Noam Sobel
Amygdala

Interactive nature of intensity and valence: correlation between amygdala and OFC

Codes the valence of experience for both pleasant and unpleasant events or the intensity of experience common to both negative and positive events, but not valence itself.

Response is related specifically to the experiential dimension of intensity, and not the associated dimensions of positive and negative valence of olfactory experience.

Anderson AK .... Sobel
Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 2003, 6(2)
Anderson AK .... Sobel
Dissociated neural representations of intensity and valence in human olfaction.
Nat Neurosci 2003, 6(2)
Orbitofrontal cortex

- The major **recipient** of olfactory projections.
- **Direct** pathway from primary olfactory cortex.
- **Indirect** pathway from the dorso-medial nucleus of the thalamus.
- Role in the encoding of reward and **hedonic** experience.

**Several anatomical and cytoarchitectural subregions**

Medial orbitofrontal gyrus in response to pleasant odors; lateral orbitofrontal gyrus in response to unpleasant odors

Anderson AK, Sobel. Nat Neurosci 2003
Olfaction is largely dependent on **sniffing**

- Sniffing (odorant present) induces oscillated activity in the olfactory bulb and piriform cortex in the temporal lobe.

- Sniffing (odorant present or absent) induces activation in the **medial and posterior** orbito-frontal gyri of the frontal lobe.

- Smell (regardless of sniffing) induces activation mainly in the **lateral and anterior** orbito-frontal gyri of the frontal lobe.

**Dissociation** between regions activated by olfactory exploration (sniffing) and regions activated by olfactory content (smell).

Noam Sobel et Al
Odorant-Induced and Sniff-Induced Activation in the Cerebellum of the Human
Role of the cerebellum in olfaction

Sniff volume is *inversely proportional* to odor concentration.

As for tactile information and other senses:
Cerebellum receive olfactory information for *modulating* the sniff, which in turn modulates *further* olfactory input.

Noam Sobel et al.
Odorant-Induced and Sniff-Induced Activation in the Cerebellum of the Human
Lateralization of emotional processing as a function of Handedness

Areas similar in RH and LH, albeit with weaker activations in the latter. OFC and insula showed stronger activation in the left hemisphere.
Males: bilateral activation of the insula. Females also activated the left OFC.

Female advantage in odor identification.

Women process lexical emotional stimuli more accurately than men: generalize to olfactory perception.

Women’s greater left OFC activation during olfactory hedonic judgments correspond with

Better verbal skills and olfactory identification
FLAVOR

Results from simultaneous stimulation of three main sensory systems:

(i) **gustatory**, i.e. chemical stimulation of the taste buds of the tongue;

(ii) **olfactory**, i.e. chemical stimulation of the olfactory epithelium, both through the orthonasal and the retronasal pathways;

(iii) **trigeminal**, through chemical, thermal and tactile stimulation of the somatosensory system, both on the tongue and on the nasal epithelium, lingual and nasal somatic stimulation.
Wine appreciation
Sommeliers
In contrast to untrained individuals, sommeliers use specific strategies to classify and recognize the qualities of a particular wine.

Critical step: wine tasting via a retro-nasal olfactory pathway
The appreciation of wine by sommeliers: a functional magnetic resonance study of sensory integration. 

Neurolmage 25 (2005) 570–578
Odor cues activate the hippocampus during SWS to a much greater extent than during wakefulness.

Memory-associated odors have access to the hippocampus during SWS.

Particular sensitivity of hippocampal networks in this sleep stage to stimuli that are capable of reactivation.

Björn Rasch, Christian Büchel, Steffen Gais, Jan Born
Odor Cues During Slow-Wave Sleep Prompt Declarative Memory Consolidation
Science9 March 2007 Vol 315
Björn Rasch, Christian Büchel, Steffen Gais, Jan Born
Odor Cues During Slow-Wave Sleep Prompt Declarative Memory Consolidation
Science9 March 2007 Vol 315
Björn Rasch, Christian Büchel, Steffen Gais, Jan Born
Odor Cues During Slow-Wave Sleep Prompt Declarative Memory Consolidation
Science 9 March 2007 Vol 315
Lesions of Olfactory Cortex

Lesions including the medial temporal lobes normal olfactory detection thresholds and discrimination odors based on intensity; deficit in discriminating odors based on identity or perform odor memory; often only when odorants are presented to the nostril ipsilateral to the lesion.

Lesions including the orbitofrontal cortex normal detection thresholds, deficits in olfactory identification, quality discrimination, and memory.

Christina Zelano and Noam Sobel
Congenital Anosmia – Kallmann’s Syndrome
There are **quantitative** more than **qualitative** differences between responses of Congenital Anosmics and Normosmics

Which role can have active and working brain areas that don’t produce a conscious sensory perception?

Domenico Montanaro et Al.
Functional MRI (fMRI) of olfactory system: persistence of brain activation to odors in Kallmann Syndrome
XXXII ESNR, Genova, 20-23 Settembre 2007
Parkinson’s diseases
PARKINSON’s DISEASE

... “The pathologic process advances in a predictable sequence, but the earliest changes, even before the motor components appeared in life, were found in the dorsal motor nuclei of the glossopharyngeal and vagus nerves, the olfactory bulb and associated anterior olfactory nucleus” ...

... “Given that at least 40% of substantia nigra cells have to die before there are clinical symptoms: the clinical motor manifestations of the IPD represent the terminal stage of a process that probably started several decades previously”...

Hawkes C
Olfaction in Neurodegenerative Disorders
Correlation between olfactory loss and duration of disease

Olfactory function in IPD patients changes in an unpredictable manner

Few IPD patients were completely anosmic; none of the patients, however, were normosmic.

Herting B ... Hummel T.  
A longitudinal study of olfactory function in patients with idiopathic Parkinson’s disease.  
Hypothesis

Increase of dopaminergic neurons in the olfactory bulb in IPD patients: increase of inhibitory, dopaminergic neurons in the olfactory bulb that may appear as the result of compensatory mechanisms to the loss of dopaminergic neurons in the basal ganglia.

This inhibition may be very strong initially, leading to pronounced hyposmia or functional anosmia. Over time, it appears possible that the dopaminergic inhibition decreases while the number of neurons in the olfactory bulb decreases.

fMRI results

Neuronal activity in the amygdala and hippocampus is reduced in PD patients.

Neuronal activity in components of cortico-striatal loops appears to be up-regulated indicating compensatory processes involving the dopaminergic system.

T. Hummel et Al.
Immunohistochemical, volumetric, and functional neuroimaging studies in patients with idiopathic Parkinson’s disease.
Montanaro D, Maremmani C, Frijia F et Al.
Internal Data: working in progress. 2009-2012
Montanaro D, Maremmani C, Frijia F et al.


Internal Data: working in progress. 2009-2012
Odor identification deficits occur in Alzheimer’s disease (AD) and mild cognitive impairment (MCI), and predict clinical conversion from MCI to AD.

Predictive utility of olfactory identification deficits for decline from no MCI to MCI and AD needs to be assessed in longitudinal studies of elderly community samples.
Investigation of medico-legal cases

If a patient denies to experience olfactory sensations although olfactory OERP are present doubt on his or her claims.

Jorn Lotsch, Thomas Hummel
The clinical significance of electrophysiological measures of olfactory function
Patients and family members showed deficits in odor identification performance in both nostrils.

Odor detection thresholds differed only between patients and healthy comparison subjects.

Neuroanatomy: both patients and their healthy first-degree family members decreased volume in the olfactory bulb and primary olfactory cortex relative to healthy volunteers.

Odor identification measures may serve as a sensitive endophenotypic vulnerability marker.
Women with Childhood Maltreatment

Enhanced activation in the posterior cingulate cortex and decreased activation in the anterior cingulate cortex.

Hypothesis of an altered processing of non-traumatic stimuli in CM patients.

Ilona Croy ..... Emilia Iannilli, Thomas Hummel
Women with a History of Childhood Maltreatment Exhibit more Activation in Association Areas Following Non-Traumatic Olfactory Stimuli: A fMRI Study.
PLoS ONE February 2010 | Volume 5 | Issue 2
New theory of Autism

A dysgenesis (or complete agenesis) of the olfactory bulbs and projection zones in the brain may lead either directly or indirectly to some instances of autism spectrum disorders. Such dysgenesis may be the primary cause or a contributing cause.

A combination of olfactory bulb dysgenesis causing (or accompanied by) dysregulation of oxytocin and vasopressin functioning, mirror neuron system deficits, and hypothalamic/autonomic dysregulation might help explain many of the seemingly unrelated symptoms in autism spectrum disorders.

David Brang, V.S. Ramachandran
Olfactory bulb dysgenesis, mirror neuron system dysfunction, and autonomic dysregulation as the neural basis for autism
Medical Hypotheses 74 (2010) 919–921
CONCLUSIONS
… “To investigate the underlying pathology, quantitative and objective methods had to be developed to evaluate smell sensation and the ability to obtain information about odors” …

… “Although useful, these tests are cumbersome, time consuming, and not always objective” …
… “Can functional imaging of the human brain be applied to elucidate the neural coding beyond gross mapping?
We think that the answer is “Yes.” …


In future:

*improvement of both spatial and temporal resolution.*
F. Frijia, H. Hlavata
Post-processing

PISA, Italy

N. Vanello, F. Vanni
Department of Information Engineering
University of Pisa. Pisa

C. Maremmani
Neurologist
Neurology Unit, Carrara

C. Anselmi, A. Bonocore
Department of Pharmacology
University of Siena. Siena

D. Montanaro, F. Lombardo, S. De Cori, R. Canapicchi
Neuroradiology Unit – FGM-CNR

D. De Marchi, P. Keilberg, M. Deiana
C. Santarlasci
F. Fabrizio
TSRM
Secretary
Nursery