TITLE: FUNCTIONAL MAGNETIC RESONANCE IMAGING OF THE OLFACTORY SYSTEM

PRINCIPAL INVESTIGATOR: David M. Yousem, M.D.

CO-INVESTIGATORS: David Alsop, Ph.D., Thomas Hummel, M.D., Ph.D., Joseph Maldjian, M.D., Paul Moberg, Ph.D., Rena Geckle

ABSTRACT

This application will use functional magnetic resonance imaging (FMRI) with odor stimulation to map the cortical locations instrumental in the processing of odors. The goals of the project will be to 1) study the effect of gender, age, and handedness on odor-stimulated FMRI maps, 2) discriminate activation that occurs with olfactory nerve vs trigeminal nerve, unilateral vs bilateral, aversive vs hedonic, and passive vs active odorant stimulation, and 3) apply the normative data to study patients with congenital anosmia, post-traumatic hyposmia, and schizophrenia. We believe that olfactory nerve stimulants will activate the right orbitofrontal, peri-insular and entorhinal regions. We predict that aversive odors will primarily activate the left orbitofrontal regions as opposed to pleasant odors. We hypothesize that trigeminal activation will have greater parietal, entorhinal and piriform cortex localization. Diminution in number of brain voxels activated corrected for overall brain volume will be present in the elderly and in males compared to females. The right hemispheric dominance will be more apparent in right-handed subjects. In the last 2 years of the grant we will investigate three disease states affecting olfaction; congenital anosmia, post-traumatic hyposmia, and schizophrenia. We believe that olfactory nerve stimulants will activate the right orbitofrontal, peri-insular and entorhinal regions. We predict that aversive odors will primarily activate the left orbitofrontal regions as opposed to pleasant odors. We hypothesize that trigeminal activation will have greater parietal, entorhinal and piriform cortex localization. Diminution in number of brain voxels activated corrected for overall brain volume will be present in the elderly and in males compared to females. The right hemispheric dominance will be more apparent in right-handed subjects. In the last 2 years of the grant we will investigate three disease states affecting olfaction; congenital anosmia, post-traumatic hyposmia, and schizophrenia. We hypothesize that patients with congenital anosmia, not having formed an olfactory nerve system, will show no significant activation with olfactory nerve stimulants, but might be hypersensitive to trigeminal stimulants. Patients who have had structural (post-traumatic) and developmental (schizophrenic) disorder of the olfactory system will have depression of and rerouting of their olfactory pathways. Schizophrenics may have hyperfunction in their left hemisphere.

To achieve these goals 48 normal subjects per year, stratified into different age, gender, and handedness categories, will undergo FMRI using different odorants, different stimulations, and different olfaction tasks. The subjects will be studied in 1.5 hour FMRI sessions and will have correlative psychophysical tests performed at the University of Pennsylvania's Smell and Taste Center. After deriving a normative database of 240 subjects, 30 subjects each with congenital anosmia, post-traumatic anosmia, and schizophrenia will be tested with similar paradigms and compared with age, gender, and handedness-matched normals. The data will be compared both qualitatively and quantitatively for sites of activation and volume of activation. We will control for brain volume variation by using SPM96 processing software and a brain volume covariate, measured from volumetric MRI sequences.

This grant will clarify the regional localization of odor processing in the human brain, adding to the existing framework provided by 1) psychophysical testing of patients with head trauma and lobectomies, 2) electrophysiologic studies 3) positron emission tomography (PET) research, and 4) animal studies. The effect of disease processes on the sense of smell are currently underappreciated, since, in fact, olfactory loss may be 1) a sensitive and early indicator of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia, and multiple sclerosis, 2) the primary deficit in Kallmann's syndrome and head trauma and 3) a comorbid component of more generalized diseases such as AIDS and cancer. This grant will provide insights into cortical routing in normal smell function and what happens to these pathways in specific disease states. Using FMRI with odor stimulation may potentially lead to earlier diagnosis of some conditions and could be used to monitor therapy or recovery of function in others.

Specific Aims:
1: In Experiment 1, we will determine the roles of age, gender, and handedness on cortical olfactory processing using functional magnetic resonance imaging (FMRI) studies with olfactory and trigeminal stimulants. We will determine whether these variables are associated with a difference in the sites and volume of brain tissue activated (corrected for regional brain volume).

Hypotheses: Hypothesis 1) The primary sites of activation using olfactory nerve stimulants will be the orbitofrontal cortices (Brodmann areas 11, 12, and 47) and bilateral anteroinferomedial (hippocampal, perihippocampal, peri-amygdaoid) and peri-insular temporal lobes (Brodmann areas 25, 28, 34, 35,
and 36). Cerebellar activation may occur as well. Subhypothesis 1: Based on our preliminary work in 19 normal subjects, the frontal and temporal lobe activation will have a right-hemispheric predilection in right-handed subjects. Subhypothesis 2: Some, but not all, left-handed subjects will show a left-sided hemispheric dominance on FMRI studies with odor stimulation. No differences in regions activated, besides this right-left difference, will be found. Hypothesis 2) Women will have greater activation (based on voxels activated and strength of activation) than men in olfactory eloquent areas. Hypothesis 3) Subjects ≤ 40 years old will have greater activation than subjects > 60 years old for the primary Brodmann areas associated with olfaction. We believe that the regional brain activity will parallel the depression of University of Pennsylvania Smell Identification Test (UPSIT) scores seen in patients over 60-70 and the better performance by women than men across all age groups.

2: In Experiment 2, we will determine whether the sites of cortical activation differ in FMRI experiments employing unilateral versus bilateral nasal stimulation, olfactory nerve versus trigeminal stimulants, and pleasant versus aversive stimulants. We wish to look at the brain under a variety of paradigms to accurately map regions of the cortex that are affected by the method of presentation, intensity, and pleasantness of the odor being presented. Hypotheses: Hypothesis 1) Based on our pilot work, we believe that there may be more activation in the right entorhinal/piriform cortex region when the right nostril is stimulated and more activation in the left entorhinal/piriform cortex when the left nostril is stimulated. Subhypothesis: The right nostril studies will more closely approximate the bilateral nostril studies. Hypothesis 2) Trigeminal nerve stimulants will yield more activated voxels in the sensory and sensory association cortices (Brodmann areas 1, 7, 40) and entorhinal cortex locations (Brodmann areas 28, 34, and 38) than olfactory nerve stimulants. Hypothesis 3) Aversive olfactory stimulants will activate the hippocampal (Brodmann area 35 and 36), amygdaloid (Brodmann area 34), and cingulate (Brodmann areas 23, 24, 29) regions more than pleasant ones. Subhypothesis 1: The ratio of left orbitofrontal/right orbitofrontal activation will be higher with aversive odorants than with pleasant odorants in right-handed subjects. These hypotheses are based on our pilot data and and PET studies utilizing painful or unpleasant stimuli that activated these areas.

3: In Experiment 3, we will examine how the brain handles odors under pathologic conditions. To do so, we will apply the normative data results acquired from Specific Aims 1-2 in the first years of the grant cycle to the study of three cohorts of patients (congenital anosmics, post-traumatic hyposmics, and schizophrenics with smell loss) in the last 2 years of the grant. We will compare FMRI results in individuals without olfactory bulbs and/or tracts (congenital anosmics), subjects who had an olfactory system but had it damaged during head trauma, and subjects with an intact system that does not function correctly (schizophrenia) with our healthy volunteers’ data. Hypotheses: Hypothesis 1) Patients with congenital anosmia will not significantly activate olfactory eloquent areas of the brain (beyond statistical noise) during passive olfactory nerve stimulation. These patients afford a unique opportunity to study olfactory paradigms without the influence of the olfactory nerve input. Hypothesis 2) Congenital anosmics will show augmentation of activation when trigeminal stimulants are used compared to age and gender matched control subjects in the relevant areas mentioned above (Specific Aim #2, hypothesis #2). Hypothesis 3) FMRI will demonstrate new sites of activation (Brodmann areas) in patients with post-traumatic hyposmia compared with congenital anosmics and matched controls. We have shown in prior work that these patients often have severe orbitofrontal lobe damage. We believe that these subjects will reroute olfactory pathways from the more damaged hemisphere to the less damaged hemisphere. Subhypothesis 1: There will be greater temporal lobe and/or parietal activation in post-traumatic subjects given the same stimuli as matched healthy subjects. Subhypothesis 2: There will be a right-left hemispheric shift in odor dominance in favor of the less traumatized hemisphere. Hypothesis 4) In patients with schizophrenia, entorhinal and piriform cortex and right orbitofrontal activation will be depressed compared to age and gender matched controls. Subhypothesis 1: The ratio of left hemisphere/right hemisphere frontal activation will be greater in schizophrenics than control subjects.

Background:

Brain Mapping using Imaging in Normal Subjects:

Despite the fact that the sense of smell is common to nearly all creatures in the animal kingdom and is centered in a portion of the brain thought to develop early in phylogeny, the understanding of odor processing and the integration of odor-associated memories and emotions is quite limited. Only a
few positron emission tomography (PET) studies [1, 2] and a few preliminary FMRI studies [3, 4] have been published using smell stimulation. These studies have shown either an increase in regional blood flow (PET) or activation of cerebral voxels (FMRI) in the orbitofrontal regions (right more than left) with odor stimulation. Koizuka et al noted bilateral increased cerebral blood flow in the inferior frontal lobes, piriform cortex, and orbitofrontal regions after phenyl ethyl alcohol odor stimulation using a dynamic first pass MR experiment employing paramagnetic contrast agents designed to study perfusion [3]. Wexler et al demonstrated similar areas of activation as well as activation of areas in the limbic system when odors were presented to normal volunteers [5]. Levy et al and Ramsey et al have also reported inconsistent activation in orbitofrontal, entorhinal, piriform, and cingulate regions using a modified gradient echo FLASH technique [6, 7]. The findings noted above have led us to our hypotheses that odors presented to right-handed subjects will primarily stimulate the right orbitofrontal and anteroinferior temporal region (Specific Aim #1, Hypothesis #1).

The effects of age, gender, and handedness on olfaction have not been addressed with odor stimulated FMRI studies. These factors are known to have strong influences on the results of psychophysical tests of olfaction [8-11] and will be addressed as part of Specific Aim #1. We believe that the FMRI studies will replicate what is seen on tests of odor identification and detection; a progressive decline in ability with age over 60 years and better performance on the part of women. The FMRI correlate will be a diminution in the volume and strength of activation after the age of 60 and decreased numbers of voxels activated in men compared with women (Specific Aim 1, Hypotheses 2 and 3). We will add a brain volume covariate to the most widely used FMRI analysis package, statistical parametric mapping (SPM96), to correct for variations in brain volumes between men and women, young and old. The volumes will be computed by the principal investigator who has extensive experience in this technique [12-15].

A number of studies have shown differences in regional brain volumes in men and women and in the effect of aging and brain atrophy between men and women [16, 17]. These volumetric issues point up the necessity of correcting for regional brain volume; 10 activated voxels in an area of brain that has only 100 voxels in it due to atrophy is different than 10 activated voxels in a region of 300 voxels. This issue will be addressed by SPM96 which allows covariates for regional brain volume. The regional metabolism of the brain as measured by PET has also been shown to differ between men and women [18, 19]. Men appear to have greater glucose utilization in the temporal lobes and cerebellum, whereas women have greater glucose utilization in the cingulate regions. Cerebral blood flow is also increased globally in women compared to men [18]. These factors may become apparent in our analysis of Specific Aim #1 and gender differences.

One PET study has suggested that regional blood flow is increased to both amygdala (left more than right) when subjectively aversive odors are used [2]. The same group has found that the left lateral orbitofrontal region shows increased regional cerebral blood flow when aversive (dimethyl sulfide, ethanediol, methanediol) odorants were compared with pleasant (fruits and spices) ones. An abstract presented at the 1997 International Symposium on Olfaction and Taste claimed that hydrogen sulfide preferentially stimulated the left orbitofrontal and piriform region using FMRI [20]. These data are supportive of the hypotheses we wish to test in Specific Aim #2.

None of the published or abstracted FMRI studies have looked at unilateral versus bilateral nasal stimulation, an issue we will address in this proposal. This issue appears to be intertwined with handedness in the literature and is quite controversial. Some investigators have claimed that right-handed individuals are more sensitive on the left side of their nose for odor detection and that left-handed individuals have a right nose preference for detection [21, 22]. Others disagree that there is a nostril preference for odor detection [23-26]. Odor discrimination has been reported to be better on the right side of the nose in all subjects [27] or just in right-handed subjects [26]. In our experience, subjects seem to do only as well with bilateral psychophysical testing as their best unilateral nostril. For this reason we expect to see little change between right nostril stimulation and bilateral stimulation (Specific Aim #2, Hypothesis 1, Subhypothesis 1).

We will attempt to clarify this confusing issue by performing FMRI with unilateral olfactory stimulation in Specific Aim #2. We have found entorhinal and piriform cortex stimulation on the ipsilateral side of the nostril presentation in 4 subjects studied by FMRI (Specific Aim #2, Hypothesis #1), but have not controlled for handedness in this regard. We will explore the issue of handedness and unilateral stimulation in this grant. At the same time, the psychophysical tests performed by the Smell and Taste Center Core may shed more light on the interactions between hemispheres, handedness, and nostrils.
As for the issues of olfactory versus pure trigeminal stimulation, we have studied this in a previous publication [28] and in a pilot study of 22 subjects [29] (see Progress Report below). Previously we compared olfactory nerve versus mixed olfactory and trigeminal nerve stimulants and found large differences between regions activated [28]. Olfactory nerve stimulants primarily influenced the orbitofrontal zones (right > left) and the cerebellum, whereas the mixed stimulants elicited a more generalized reaction. Carbon dioxide trigeminal stimulation activated parietal somatosensory regions of the brain (Brodmann areas 1, 7, 40) and brainstem sites. In Specific Aim #2, we wish to further explore the effects of olfactory versus trigeminal nerve stimulants to better understand the two components of intranasal sensation. Our prior results with carbon dioxide led to hypothesis 2 of Specific Aim #2; parietal and entorhinal/piriform cortex activation will be more prominent with trigeminal stimulants than with olfactory nerve stimulants. We believe that we will see entorhinal and piriform cortex activation with both types of stimulants, however.

A poster presented at the 1997 International Symposium on Olfaction and Taste suggested that sniffing induces entorhinal cortex activation [30]. The authors found that simulating sniffing with air flow devices will cause a similar activation. These results duplicate electrophysiological findings in mammals where sniffing induces an oscillation of activity in the piriform cortex. The authors suggested that the primary component of entorhinal and piriform cortex activation associated with olfaction may not be due to olfactory nerve stimulation, but may be due to trigeminal influences. Although these findings support support our related hypotheses, we have noted only a minor effect of sniffing when we performed a pilot study of 6 subjects using the Burghart Olfactometer which does not require sniffing for odor presentation. We found that activation of the entorhinal and piriform cortices occurs without sniffing. These processes will be explored in greater detail (see below) using our control group of congenital anosmics in Specific Aim #3.

**Brain Mapping using Imaging in Disease States:**

No studies on FMRI, olfaction, and illnesses have been published, but a few have been presented at meetings. Levy et al have looked at 10 patients with hyposmia and 5 with phantosmia using FMRI [31, 32]. No or depressed activation was seen in the patients with hyposmia whereas those with phantosmia had elevated activation levels with imagined odors compared to controls. The sites of activation were not specified in the abstract.

We have also reported at a meeting our results with FMRI in 5 individuals with early Alzheimer's disease. We have found a complete absence of activation of "olfactory eloquent" areas of the brain when phenyl ethyl alcohol is used as the odorant [33].

To date no one has used FMRI to explore even the most basic group of patients who have olfactory deficits--those with congenital anosmia. Patients who have a known single event that affects their sense of smell and transsects the olfactory pathways (post-traumatic patients) and those with a neuropsychiatric disease that affects olfaction at a young age (schizophrenia) have also not been explored with smell-stimulated FMRI. This is despite the fact that a large literature is available describing the olfactory deficits in these subjects [12, 14, 34-48].

Based on our experience with morphologic imaging of patients with congenital anosmia [12, 49] (see Preliminary Data below) we hypothesize that patients without an olfactory bulb or tract will not activate their olfactory system, but that the trigeminal innervation will be intact (Specific Aim #3, hypotheses 1 and 2). A recently published study has shown that perception and discrimination of "trigeminal" odors may be intact in patients with congenital anosmia [50]. They found that anosmic subjects (Kallmann's patients) scored only slightly worse than normosmic controls on tests of trigeminal stimulant discrimination. However a report by Hummel et al found that Kallmann's syndrome patients had hypersensitivity of the trigeminal nerve as measured by chemosensory evoked potentials [51]. We believe that our FMRI results will duplicate the findings of Hummel et al and that we will see increased brain activation after trigeminal stimulation in congenital anosmics compared with controls (Specific Aim #3, hypothesis 2).

With respect to patients with post-traumatic hyposmia [14], we have seen that damage to the olfactory bulbs and tracts in head trauma patients is accompanied by frontal lobe injury in 61% of cases and temporal lobe injury in less than one third of patients. We therefore believe that rerouting away from damaged areas in the frontal lobes may take place in those head trauma patients who have residual olfactory function (Specific Aim #3, hypothesis 3).

A number of PET studies have looked at the schizophrenic population under non-olfactory conditions. There appears to be a discrepancy in oxygen utilization and/or regional blood flow between the left hemisphere and the right hemisphere [52]. The left side appears to be "functionally overactive" in schizophrenics [52-55] (Specific Aim 3, Hypothesis 4, Subhypothesis 1). Hypermetabolism in
dopamine pathway components has also been reported [55]. Differences in regional volumes of the brain in schizophrenics have been associated with subtypes of schizophrenia with and without "negative symptoms" [56]. For these reasons, we wish to explore this patient population with FMRI as part of Specific Aim #3 (Hypothesis 4). Because of the potential for the aforementioned differences in regional brain volumes, we will correct for these effects using SPM96 software and a covariate of brain volume.

**Brain Mapping using Non-Imaging Techniques in Animals:**

Animal studies employing electrophysiology and axonal tracing have provided the basis of the central olfactory circuitry. Numerous authors have described connections within the olfactory system between the olfactory bulb and the thalamus, diencephalon, piriform cortex, hippocampus, caudal hypothalamus, cingulate gyrus, orbitofrontal regions, and amygdala in different species of mammals and non-mammalian animals [57-63]. Carmichael et al have shown that axonal tracers placed in the macaque bulb will label its projections to the piriform cortex, the amygdala, the periamygdaloid region, and the entorhinal cortex, in addition to other areas [59]. The periamygdaloid area, entorhinal cortex (Brodmann area 28) and perirhinal area (Brodmann area 35) were shown to receive fibers from the bulb and nucleus in other studies as well [64-66]. The fibers of the prepiriform cortex lead to the amygdala [67]. In Old World monkeys, Porrino et al have shown connections from the amygdala to the orbitofrontal cortices [68]. When the entorhinal cortex of the monkey undergoes electrical stimulation, the orbitofrontal cortex shows evoked potentials [69, 70]. The medial dorsal nucleus of the thalamus of monkeys also receives afferents from the temporal lobe olfactory eloquent areas and passes projections to the frontal lobes [58, 60, 67, 71, 72]. The entorhinal cortex sends fibers to Brodmann areas 21, 22, 36, 37, 38 and to the dentate gyrus of the hippocampal formation [73]. While the studies cited above provide a framework for mapping odor detection and neuronal pathways, the application of these results to odor-processing in man has been limited. Nonetheless most of these studies support the hypotheses we project for Specific Aim #1, Hypothesis 1.

**Brain Mapping using Non-Imaging Techniques in Humans:**

In man, mapping of the brain's handling of odors has been derived from patients who have had brain damage from head trauma and in patients undergoing surgical resection of lobes of the brain. The latter has proven more fruitful since the brain damage studies [14, 39] have suffered from a high rate of anosmia and multiple foci of injuries in the patients examined [14]. Performance on tests of olfaction pre- and post-operatively have suggested that odor memory is impaired in patients who have had excision of the right temporal or right orbitofrontal cortex [74].

Amygdlectomy in patients who have unpleasant olfactory auras associated with their seizures relieves the olfactory disturbance [75]. We therefore believe that the amygdala will be selectively activated when odors that are unpleasant are utilized in our paradigms (Specific Aim #2, hypothesis #3). Furthermore, if a right frontal lobectomy spares the orbitofrontal region (Brodmann's area 11), odor identification defects have been reported to be minimal [76] in one study whereas our group has found a strong effect (see Preliminary Data, Project #1 of this Program). Conflicting data have also been presented regarding odor detection thresholds [76, 77]. Some say they are unimpaired even with complete lobectomies [76] while we have obtained conflicting results (see preliminary data, Project #1 of this Program). We have left temporal lobectomies.

**Significance:**

What is the value in studying cortical maps of olfaction? In addition to expanding the understanding of how the brain works and what circuits are integrated for a normal sense of smell, mapping of olfactory centers has important clinical implications. Patients suffering from dysosmia and anosmia are sometimes incapacitated by the disability associated with their chemosensory dysfunction. This can even affect the nutritional status of the individual, as he or she fails to obtain the proper nutrition due to the unpleasant odors associated with food intake [78]. Knowing the potential sites for inducing changes in one's sense of smell prior to operating would be useful for surgeons who operate in the orbitofrontal regions (for craniofacial resections of head and neck cancers or skull base neoplasms like meningiomas) and periamygdaloid zones (for seizure focus or neoplasm resections). Specific deficits in olfaction may be shown to correlate with specific sites in the brain by FMRI and may help neurologists better localize disease processes in advance of imaging.

There are also a whole host of diseases that can affect the sense of smell. Many of these diseases are neurodegenerative in nature and, since the sense of smell is affected in the aging process, FMRI data stratified by age will provide a framework upon which to study such entities as Alzheimer's disease, Parkinson's disease, Huntington's chorea, multiple sclerosis, Wernicke's...
encephalopathy, and Korsakoff's psychosis [78-83]. We have already demonstrated in pilot data the marked diminution in brain activation under passive conditions of smell stimulation in subjects with Alzheimer's disease. We believe that this work is a stepping stone to the screening of individuals at risk for developing Alzheimer's disease (e.g. with apolipoprotein-E karyotype E-4 or with early memory loss) or other neurodegenerative disorders that affect olfaction. Already psychophysical tests have been able to identify a patient population at risk for developing Alzheimer's disease [84]. We have also noted a near perfect correlation between the number of multiple sclerosis plaques in presumed "olfactory eloquent" regions and deficits on odor identification tests [81]. As multiple sclerosis is the most common neurological disease in the young (along with schizophrenia and head trauma which we intend to study) and Alzheimer's disease is one of the most common in the elderly we believe that pursuing imaging tests of olfaction is critical in understanding neuropsychological pathogenesis. Olfactory stimulated FMRI may be able to detect brain deficits in patients with many of these neurological diseases at an earlier stage where pharmacologic intervention may be of benefit.

A loss of the sense of smell may also be a comorbid component of more generalized diseases such as AIDS and cancer. This grant will provide insights into how the brain is affected by these illnesses that secondarily affect olfaction. Olfactory stimulated FMRI could be an effective means to monitor therapy or recovery of function in some illnesses.

Before tackling these goals, we must know as much as possible about the brain, aging, olfaction, and the paradigms that best test the sense of smell. We will be able to design better and more succinct tests for the impaired after first studying the healthy subjects. The work with the hypomictic and anosmic subjects in this grant will lead to more effective paradigms designs for other patient groups.

**Preliminary Data/Progress Report**

**Olfactory FMRI studies**

We have recently published a pilot study of olfactory-stimulated FMRI in 5 normal right-handed males (ages 29-43) who scored 19 or 20 out of 20 on the 20 item (2 booklets) UPSIT test or 38-40 on the 40 item (4 booklets) test [28]. (Appendix 1)

Localization for the FMRI studies utilized a sagittal T1-weighted scan. FMRI studies were performed in an axial plane using multislice gradient echo echoplanar imaging using a blood oxygen level dependent (BOLD) experimental paradigm on a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WS, USA) retrofitted with Advanced NMR hardware (ANMR, Woburn MA, USA) at the Maudsley Hospital, London. In each of 10 contiguous planes parallel to the anterior commissure-posterior commissure line (AC-PC), 100 T2*-weighted MR images depicting BOLD contrast were acquired with time to echo (TE) = 21-40 msec, repetition time (TR) = 3000 msec, in-plane resolution = 3 mm, slice thickness = 5 mm [85]. The TEs were varied in 3 individuals in order to optimize visualization of the inferior temporal and frontal lobes (reducing the TEs decreased susceptibility at the skull base, but doing so may also decrease sensitivity to BOLD effects). A high resolution inversion recovery echoplanar T2-weighted image was performed to facilitate post-processing registration of the FMRI data in standard space.

The task paradigm consisted of alternating rest-stimulus cycles (30 seconds rest, 30 seconds stimulus) over the 5 minutes. Olfactory stimuli were presented using a custom-built olfactometer. The individual in the magnet inhaled the odor-laden air through both nostrils. Two sets of odorants were used on 2 different days, spaced one week apart. The odors employed for the first week were eugenol, geraniol and methyl salicylate designed as predominantly olfactory nerve mediated odorants. Twenty five milliliters of each effluent were placed in an individual reservoir tube. These three odors were chosen because less than 15% of anosmic individuals with no olfactory nerve function can detect these odors, suggesting that there is very little trigeminal nerve stimulation by these odors [10]. In the second week, odors with stronger trigeminal stimulation (ylang ylang, patchouli, and rosemary oil) were utilized. The trigeminal influence of these odors was corroborated by each subjects' confirming a burning, irritating sensation in the ipsilateral nostril when presented with the odor unilaterally. This is a standard method for verifying trigeminal stimulation with odorants [75, 86, 87].

Each subject underwent two separate identical series of scans for each set of odorants in the axial plane (to assess intrasubject variability and accommodation versus amplification). The two scans were spaced approximately 5 minutes apart (delayed for data retrieval) without subject movement or change in scanning variables. Overall time in the scanner was approximately 35 minutes per subject for each session.
For group-averaged activation maps, generically activated voxels were colored and overlaid on the high resolution EPI template image in Talairach space, and represented as a series of oblique axial slices in the AC-PC plane to form a generic brain activation map (GBAM). These displays allowed the identification of the standard Talairach stereotactic coordinates and approximate Brodmann areas for each regional focus of generic activation.

The olfactory nerve paradigm (methylsalicylate, eugenol, and geraniol) produced extensive activation that was predominantly localized to the orbitofrontal region (Brodmann area 11) and the cerebellum. (see Table 1) The right orbitofrontal region had by far the greatest degree of activation and the highest median fundamental power quotient (FPQ) values.

Table 1: Results with methyl salicylate, eugenol, geraniol (primarily olfactory nerve mediated) odorants

<table>
<thead>
<tr>
<th>Size of activation (in voxels)</th>
<th>FPQ value (see above)*</th>
<th>Brodmann Area #</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>43, 16</td>
<td>2.5, 2.1</td>
<td>11</td>
<td>Right orbitofrontal</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>11</td>
<td>Left orbitofrontal</td>
</tr>
<tr>
<td>10</td>
<td>2.1</td>
<td>Not described</td>
<td>Cerebellum</td>
</tr>
</tbody>
</table>

*FPQs over 2.0 considered statistically significant (FPQs over 2.0 correlate to a Type I (false positive) error rate of p = .005)

The second exposure to these stimuli showed diminished activation relative to the first experiment suggesting odor accommodation. The number of voxels activated in the orbitofrontal (Brodmann area 11) region declined by 31.6% between the first and second exposure.

The presence of orbitofrontal activation strengthens our hypotheses that it is instrumental in odor detection and identification paradigms in fMRI (Specific Aim 1, hypothesis 1). We believe the cerebellar activation that was found may reflect the attentional activation that has recently been credited to the cerebellum that is independent of motor processes [88] (Specific Aim 1, hypothesis 3). The importance of this early work was to demonstrate a technique that can quantify the degree of activation by number of voxels in a Brodmann area that are activated. The quantification aspect will be critical to showing age and gender, right and left sided, and normal volunteer and patient subject differences across regions of interest.

The paradigm with mixed olfactory nerve and trigeminal nerve odorants showed wider activation of many different areas, including visual, precuneus, and cingulate areas (see Table 2). Orbitofrontal activation was less conspicuous but was still predominantly right-sided.

Table 2: Results with ylang ylang, rosemary oil, patchouli (olfactory and trigeminal nerve mediated) odorants

<table>
<thead>
<tr>
<th>Size of activation (in voxels)</th>
<th>FPQ value (see above)*</th>
<th>Brodmann Area #</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>2.5</td>
<td>19</td>
<td>Left primary visual cortex</td>
</tr>
<tr>
<td>58</td>
<td>2.2</td>
<td>30</td>
<td>Retrosplenial cortex</td>
</tr>
<tr>
<td>53</td>
<td>2.8</td>
<td>19</td>
<td>Right primary visual cortex</td>
</tr>
<tr>
<td>49</td>
<td>2.1</td>
<td>23</td>
<td>Posterior cingulate</td>
</tr>
<tr>
<td>34</td>
<td>2.1</td>
<td>not provided</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>24</td>
<td>2.5</td>
<td>6</td>
<td>Premotor and supplemental motor cortex</td>
</tr>
<tr>
<td>22</td>
<td>2.1</td>
<td>7</td>
<td>Precuneus</td>
</tr>
<tr>
<td>22</td>
<td>2.1</td>
<td>not provided</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>21</td>
<td>2.2</td>
<td>11</td>
<td>Right orbitofrontal cortex</td>
</tr>
<tr>
<td>15</td>
<td>2.2</td>
<td>5</td>
<td>Right superior parietal lobe</td>
</tr>
<tr>
<td>10</td>
<td>2.1</td>
<td>40</td>
<td>Left supramarginal gyrus</td>
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<tr>
<td>8</td>
<td>2.2</td>
<td>21</td>
<td>Right middle temporal gyrus</td>
</tr>
</tbody>
</table>

*FPQs over 2.0 considered statistically significant (FPQs over 2.0 correlate to a Type I (false positive) error rate of p = .005)

The temporal and parietal lobe activation that is present on the mixed olfactory and trigeminal nerve studies above has been duplicated in our isolated trigeminal nerve stimulation paradigms and is the basis for our hypothesis # 2 of Specific Aim #3.

The second exposure to these stimulus produced increased activation relative to the first exposure, suggesting amplification of stimulation. The total number of voxels activated increased by 623%. Most of that increase was in the posterior cingulate (Brodmann area 23), precuneus (Brodmann area 7), superior parietal (Brodmann area 5), and visual (Brodmann areas 18 and 19) cortex.
These studies have shown that quantitative FMRI can be performed about which one can make statements regarding the volume of the brain activated and the changes induced from one paradigm to the other.

Most recently we have performed FMRI studies using a Burghart OM4-B olfactometer (Wedel, Germany) with a continuous flow method (4 liters/min) to ensure reproducible, reliable stimulation. With this technique, we have performed 31 studies on the 1.5 Tesla magnet and 16 studies on the 4.0 Tesla magnet. Four of the subjects were left-handed, and 6 were over 55 years old. Of the normal subjects that have been studied, 16 were men and 13 were women, ages 20-75. Odor stimulation was performed with the assistance of Dr. Thomas Hummel who controlled the Burghart OM4-B olfactometer and provided 1 second puffs of stimulants every 5 seconds. In the normal subjects we looked at brain activation maps under conditions of olfactory nerve (odorants = hydrogen sulfide and phenyl ethyl alcohol) (see figure 1), trigeminal nerve (odorant = carbon dioxide) (see figure 2), and mixed olfactory nerve and trigeminal nerve (odorant = benzaldehyde) stimulation (see Figure 3) [29].

We identified prominent activation in the right orbitofrontal regions (Brodmann areas 11, 12, and 47) and right anteroinferior temporal lobes (Brodmann areas 25, 28, 34, 35, and 36) using olfactory nerve (odorants = hydrogen sulfide and phenyl ethyl alcohol) and mixed olfactory nerve and trigeminal nerve (odorant = benzaldehyde) stimulation. Using benzaldehyde, we have noted a propensity for anteromedial thalamic stimulation on the right as well. With carbon dioxide more anterior temporal lobe stimulation (Brodmann areas 1, 7, 40), bilateral frontal (Brodmann areas 11, 12, and 47), and cingulate (Brodmann areas 23, 24, 29) activation has accompanied active brainstem stimulation [29]. These findings support our hypotheses in Specific Aim #2.

We found greater right frontal and peri-insular activation in women (n=7) than men (n=12) agreeing with our hypotheses of Specific Aim #1 though we did not correct for age or handedness due to our small sample sizes (see Figure 4). Older male subjects had negligible activation in olfactory eloquent regions and differed with younger male subjects who demonstrated frontal and temporal activation (see Figure 5). We found ipsilateral activation in the anteroinferolateral temporal lobe when unilateral nostril stimulation was employed with olfactory nerve odorants (see Figure 6). No frontal lobe discrepancies were noted, but this nostril pilot work did not control for age, gender or handedness. Right handed subjects showed a strong right frontal and right temporal lobe preference. A composite map of 3 left-handed subjects studied failed to show such right-sided activation (see Figure 7). These results, though preliminary, fortify the hypotheses we have proposed for Specific Aims 1 and 2.

We have now performed FMRI with odor stimulation on 2 patients with congenital anosmia (both of whom showed no significant activation with olfactory nerve stimulants and spotty activation with trigeminal stimulants), 2 patients with post-traumatic hyposmia, 1 patient with schizophrenia, 5 patients with Alzheimer's disease (4 of 5 with no significant activation with olfactory nerve stimulants), and 3 patients with Parkinson's disease (activation varied with UPSIT scores).

Other members of our FMRI group (Drs. Alsop and Maldjian) have experience performing FMRI studies on neurosurgical patients with gliomas [89, 90], subjects with epilepsy [91, 92] and healthy volunteers under paradigms of cognitive processes for learning and working memory [93, 94].

Morphologic studies:

Normative data

The purpose of including the morphologic studies listed below in our progress report is to emphasize the considerable expertise and experience we have in addressing issues as they relate to the normal subjects and the 3 patient groups we wish to study. We have gained a good rapport with our subjects and expect recruitment to be well-accepted. These studies also demonstrate our expertise in performing regional brain volume analysis with structures as small as the olfactory bulbs and tracts and as large as the temporal lobes, which will be required for volumetric analysis of regional/whole brain activation.

Our normative data work on the volume of olfactory bulbs and tracts has shown excellent reliability and accuracy for measuring the olfactory bulbs and tracts (OBTs) and temporal lobes (TLs). We assessed the reliability and reproducibility of volumetric measures of OBTs and TLs using multiple phantoms and calculating the intra- and interobserver variability of patient OBT and TL volumes using multiple readers with repetitive measurements [15]. Intraclass and Pearson correlation coefficients and mean percent differences were calculated. The measured phantom volumes were within 1.9% to 12% of true volume with variability ≤ 5%. Intraclass and Spearman correlation coefficients were ≥ 0.919.
for multiple readings by each reader and $\geq 0.924$ for measurements between readers. The mean percent inter- and intraobserver variabilities volumes were $\leq 4.2\%$ for TL and $11.3-14.6\%$ for OBTs. The higher value for the OBTs is due to the fact that the mean OBT volume measured is approximately $120 \text{ mm}^3$, therefore inclusion or exclusion of small numbers of voxels of tissue (each of which has a volume of just under $0.7 \text{ mm}^3$) can make a huge variation between reviewers. We have thus demonstrated that reproducibility of volumetric measures of the olfactory apparatus is excellent with high intraobserver and interobserver correlations. The whole brain and regional brain volumes areas to be studied in this grant are many times larger than the OBTs and are expected to yield variations under $5\%$ between and among reviewers.

After establishing the reliability and accuracy of our testing methods, we have established preliminary norms for OBT volumes across age groups. Since the sense of smell shows a diminution with age as measured by the UPSIT, we sought to determine if the volumes of the olfactory bulbs and tracts (OBTs) and the temporal lobes (TL) declined in parallel to smell function. To do so, we measured the OBT volumes of 36 individuals ranging in age from 22 to 78 who did not complain of any loss of the sense of smell. The OBT volumes showed an initial increase to the 4th decade of life and then a decrease with increasing age while the trend in TL volume was not as dramatic [13]. These normative data can be used to assess the OBTs of cohorts of patients with neurodegenerative disorders that affect olfaction.

**Disease States**

**Post-traumatic:** To evaluate the sites of injury in patients with post-traumatic olfactory deficits, we initially studied 25 patients with post-traumatic smell dysfunction utilizing olfactory testing and MR [14]. Quantitative and qualitative gradings for olfactory bulb, tract, subfrontal region, hippocampus, and temporal lobe damage correlated with olfactory test results. Twelve patients were anosmic, 8 had severe impairment, and 5 were mildly impaired. Olfactory bulb and tract (88% of patients), subfrontal (60%) and temporal lobe (32%) injuries were found (figure 3 and 4), but did not correlate well with the UPSIT scores. Odor discrimination deficits correlated best with frontal injury and odor memory with temporal lobe damage. MR detected abnormalities in patients with post-traumatic olfactory dysfunction at a very high rate (88%), predominantly in the olfactory bulbs, tracts, and inferior frontal lobes, but qualitative and quantitative assessments of damage showed inconsistent correlations with olfactory tests.

In a follow-up study, we increased the number of post-traumatic hyposmic individuals to 20 subjects; 16 were anosmic. Correlations were computed between the OBT and TL volumes and the patients' scores on tests of odor identification (UPSIT), detection, and memory with Spearman rank correlation coefficients. Mann Whitney tests were used to compare volumes between control subjects and post-traumatic patients. OBT (89% of patients), subfrontal (61%) and TL (31%) injuries were found. Bilaterality to the OBT and frontal lobes injury was present in 89% of the cases. With the recruitment of more subjects that had residual olfactory function, we found that the left OBT volume showed a statistically significant correlation with left UPSIT scores and threshold values before and after correction for age. The right OBT volume correlated with right odor memory scores after correction for age effects. There was a statistically significant difference in the right and left OBT volumes between anosmic and hyposmic patients and between post-traumatic patients (anosmic, hyposmic, and all post-traumatic patients) and controls. Intraclass correlation coefficients for multiple measurements by and between observers were above 0.92 for all OBT and TL volumes. We concluded that while some correlations can be made between sites of injury and olfactory tests, the high rate of "multiple hits" and bilateral injuries suggested that other methods (such as functional magnetic resonance imaging) may be better suited to mapping the olfactory system.

**Congenital anosmia:** In our study of 24 individuals with congenital anosmia, we demonstrated absence of the olfactory bulbs and tracts in 16 patients (figure 5), hypoplasia of bulbs and tracts in 4 patients, and absent bulbs but hypoplastic tracts in the final 4 patients. Three individuals could smell, though with severe deficits (UPSITS 18-24), and 2 of the 3 had intact small bulbs and tracts [12, 95]. Volumes measured showed outstanding intra- and inter-observer agreement (0.86-0.96 intraclass correlations). Using a phantom for reliability showed interobserver variation between 0.1% and 4.8%.

Using patients with congenital anosmia and no bulbs or tracts in our project allows us to eliminate the effects of the olfactory nerve on our FMRI paradigms and provides us with an outstanding control group. Thus we can compare activations between normosmic patients and congenital anosmics to study the trigeminal influences on sniffing, aversive odors, and unilateral
Neuropsychiatric disorders: Odor identification, detection threshold, and memory are impaired in patients with schizophrenia and are unassociated with neuroleptic usage, cognitive dysfunction, or severity of illness. Dr. Paul Moberg (co-investigator) has recently completed a study comparing 16 elderly schizophrenic patients, 20 patients with Alzheimer's disease and 20 healthy age matched controls. The schizophrenic patients had severe deficits in odor identification, similar to the Alzheimer's patients [96]. Males performed worse than women on UPSIT testing. Dr. Moberg has also shown that the degree of olfactory deficit correlates with the duration of schizophrenia, suggesting a progressive decline of olfactory abilities.

Electrophysiologic studies:

Dr. Thomas Hummel of our group has noted a diminution in the mean amplitudes of chemosensory event-related potentials in elderly subjects for both olfactory nerve and trigeminal nerve stimulants (Hummel T in press to Electroenceph Clin Neurophysiol). Latencies for N1 also increased with increasing age. These electrophysiological data support the hypotheses of Specific Aim 1 that one would expect diminution in brain activation measured by FMRI with increasing age. Dr. Hummel also found that females had larger mean chemosensory event-related potential amplitudes than men. Again these data support our contention that we will see more voxels per brain volume activated in women when we compare their FMRI results with those of men.

Electrophysiologic studies have reported shorter latencies and smaller amplitudes in the left nostril compared with the right nostril using carbon dioxide, menthol, and hydrogen sulfide stimulants [97]. Vanillin had shorter latencies and smaller amplitudes on the right compared with the left but was also graded favorably on the pleasantness scale. These issues of lateralization and the sidedness associated with pleasant or unpleasant, olfactory or trigeminal odorants will be addressed in Specific Aim 2 of this FMRI study.

Dr. Hummel has also recently shown that patients who have congenital anosmia have higher mean amplitudes than controls when given trigeminal stimulants [51]. These findings in patients with congenital anosmia are different than those seen in patients with acquired hyposmia or anosmia. They have lower mean amplitudes of event related potentials than healthy individuals when given a trigeminal stimulant [98]. These results suggest that congenital anosmics will have higher sensitivity to trigeminal stimuli, whereas patients (such as those with head trauma or schizophrenia) may show a decrease in responsiveness to trigeminal nerve stimulants. These issues will be studied in Specific Aim #3. All three groups will undoubtedly have a decreased number of voxels activated with olfactory nerve stimulants compared to age- and gender-matched controls.

Research Design and Methods:

We will describe our recruitment techniques, the psychophysical olfactory tests that will be performed, and the FMRI protocols to be used for all patients. Then we discuss how each of our Specific Aims will be fulfilled by the protocols performed and what statistical analyses will be used.

Recruitment:

Control subjects will be recruited through the use of advertisements in local newspapers, the Veteran's Hospital of Philadelphia volunteer registry, and signs posted in the Delaware Valley area. These notices will provide a central phone number for recruitment of subjects monitored daily by the Research Coordinator (RC) or Principal Investigator (PI). Many of the control subjects can be obtained from the current data base of the Core of the Smell and Taste Center and will be called by the RC. The RC or PI will screen the subjects for any possible causes of smell dysfunction prior to inviting the subjects to enter the study. The subjects will complete a handedness survey (Appendix 2) to insure that they will be appropriately placed into the correct category of subject. The Research Coordinator will maintain a database for the subjects so that the proper combination of males and females and different age brackets and left-handed and right-handed individuals can be studied (see below). Since the graph of the age vs UPSIT scores seems to level off from ages 40 to 60 [78] the goal will be to obtain an equal number of men and women in subgroups of < 40 years old, 40-60 years old, 61-70 years old, and > 70 years old. In this way we will capture subjects that are beginning to lose odor identification function (61-70 year olds), and those with more severe deficits (> 70 year olds) as well as those who may still be on the ascending limb of odor identification ability (<40 years old). These groups can be restratified if trends within groups are noted or for statistical purposes (power calculations).
The patients with congenital anosmia will be recruited from the databases of patients already studied at the Smell and Taste Center (STC). We have already examined over 30 individuals with congenital anosmia with volumetric MR reported in a prior publication [12]. These patients have experienced being in the MR magnet and are likely to be willing to undergo the FMRI protocol. They must score ≤ 18 on the 40 item UPSIT test to qualify for this project. We will only invite those individuals less than 50 years old (28 of the 30 already studied) for this study, since by UPSIT testing the age and gender matched controls less than 50 years old should have excellent senses of smells (UPSIT scores exceeding 35).

We have good rapport with a group of 36 subjects who have post-traumatic smell loss who have been studied previously with MR [14]. Twenty five of these subjects are currently under 50 years old and they should be willing to participate in the proposed study. The Smell and Taste Center sees several individuals with hyposmia secondary to head trauma as part of its clinical service and we believe that we will be able to easily recruit the subjects needed to fulfill Specific Aim 3. We shall only include those subjects with UPSIT scores of 20-30 out of the 40 item test. Again, we will study only those less than 50 years old to eliminate age effects on the sense of smell.

Dr. Paul Moberg has studied a large cohort of patients with schizophrenia through his appointment in the Department of Psychiatry. He has experience in studying this patient population [99-102] and will help recruit subjects to fulfill the goal of studying 30 schizophrenic individuals. These subjects must have a smell deficit within the range of UPSIT scores between 20-30. We will eliminate those who may be anosmic (UPSIT ≤ 18) and those who may be near normal for age (> 31). We will endeavor to recruit subjects who are less than 50 years old since by UPSIT testing the age and gender matched controls should have excellent senses of smell with UPSIT scores exceeding 35. Since Turetsky et al. have shown differential regional cerebral blood flow in different types of schizophrenics, we will only recruit subjects that are moderate in their severity. The following four standardized rating scales will be used to assess symptom severity by Dr. Moberg: Negative Symptoms, Disorganization, Schneiderian Delusions and Hallucinations, and Suspicion-Hostility. Patients will be subtyped as either deficit or nondeficit on the basis of enduring negative symptoms.

Over the 5 years of the grant we expect to recruit patients with the following attributes:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Right-handed men</th>
<th>Right-handed women</th>
<th>Left-handed men</th>
<th>Left-handed women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>&lt; 40*</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>60</td>
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<td>60-70*</td>
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<td>10</td>
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<td>60</td>
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<tr>
<td>&gt; 70*</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Anosmic**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>30**</td>
</tr>
<tr>
<td>Post-traumatic**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>30**</td>
</tr>
<tr>
<td>Schizophrenic**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>30**</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>330</td>
</tr>
</tbody>
</table>

* predominantly in 1st three years of grant
** 4th and 5th year of grant. Availability of subjects will dictate age, gender, and handedness divisions. In general, we find more young male post-traumatic subjects and more young female schizophrenic subjects.

The Research Coordinator, Principal Investigator and/or Dr. Paul Moberg will review the consent forms with the subjects who will be considered for the FMRI protocol. At that time patients who have severe claustrophobia, pacemakers, metal implants, and a history of metal in the eyes will be excluded from the study. We may require plain films on some subjects to exclude metal in the eyes. For the control subjects, we will ask questions to ensure that they have not had significant head trauma or sinonasal infections that may affect the sense of smell. Dr. Moberg will design a few standard questions that might give a hint as to whether the "control" subjects could have occult schizophrenia. The patients with congenital anosmia, post-traumatic hyposmia, and schizophrenia will be quizzed to ensure that no other cause for their olfactory loss is likely besides that category for which they were recruited. We will employ the standard STC patient surveys to make this determination. Women will be asked to have urine or blood pregnancy tests performed and documented by the RC or PI within 5 days prior to MR scanning in order to ensure they are not pregnant. We will use our handedness questionnaire (Appendix 1) to verify that the subjects are right or left-handed as they had indicated during our preliminary recruitment conversation with them. The subjects will be told that they must
pass a battery of tests of their sense of smell before they will be able to proceed with the functional MRI portion of the grant.

**Olfactory testing:**

A standardized battery of three olfactory tests will be administered and are described in detail in the Core portion of this grant. Each side of the nose will be tested separately. These tests will include the UPSIT, the phenyl ethyl alcohol single staircase odor detection threshold test [103, 104], and the 24-item version of the 12-item Odor Recognition Memory Test used in our laboratory [105]. For the present purposes, two booklets of the UPSIT will be administered to the left nostril and two booklets to the right nostril, with the booklets systematically counterbalanced among subjects.

After these psychophysical tests, the subjects will be tested using the FMRI compatible olfactometer. At that time, various odors will be used to ascertain which odors the subjects will rate as being neutral in pleasantness versus unpleasant versus very pleasant smelling. The subjects will fill out questionnaires for each of the odorants tested (See Appendix 2). This will help us plan for which odors to use for the FMRI sequences below. We will use neutral odors graded 4-6 on a 10 point pleasantness scale when looking at tests of olfactory nerve vs trigeminal nerve, unilateral vs bilateral, sniffing vs non-sniffing tests. We will use odorants graded 1-3 and 7-10 to study unpleasant vs pleasant odorant stimulants respectively.

**MR study protocol:**

Localization for the FMRI studies will consist of a 500/11/1 (TR/TE/nex) T1-weighted (T1W) sagittal scan (1.5 minutes) followed by axial 500/11/1 192 X 256 5 mm interleaved scans (7.0 minutes) through the entire brain. These scans will be used to obtain regional volumes of the brain and to serve as the templates upon which to project the FMRI activation maps. A 6.0 minute coronal (500/11/1, 256 X256, 3 mm interleaved) scan will be performed through the olfactory bulbs and tracts to assess their integrity and volume. An axial single shot fast spin echo fluid attenuation inversion recovery 3 mm interleaved 55726/95.3/.5 192 X 256 scan will also be performed as a screen for intracranial disease and as the sequence to be used for volumetric analysis of the whole brain (3 minutes).

Functional MRI studies will be performed in the coronal and axial planes using multislice gradient echo echoplanar imaging. Scan parameters include a 64x64 matrix, 24 cm FOV, TR of 3000, TE 30, 5 mm thickness, and a 90 degree flip angle, delivering a voxel resolution of 4 x 4 x 5 mm. A total of 120 images will be acquired at each of 24 slice locations per run over the course of 6 minutes. The conventional T1-weighted axial images will be used for performing anatomic overlays. The task paradigm will consist of alternating rest-stimulus cycles (30 seconds each) over the 6 minutes. Following the FMRI scan, an echoplanar chemical shift imaging sequence is performed to measure the magnetic field within the brain of the subject. This information is used to correct for spatial shifts and distortion in the echoplanar images that can cause misalignment with the T1-weighted anatomic images. This distortion correction scan and the use of lower TEs (30 msec) can help to reduce susceptibility artifacts at the skull base.

Olfactory stimuli will be presented by Dr. Thomas Hummel using a Burghart OM4-B olfactometer (Wedel, Germany) with a continuous flow method (4 l/min). Stimuli will be performed for 1 second every 3 seconds in a 30 seconds on, 30 seconds off room air protocol. The olfactometer will be equipped with a nozzle which can present 4 different odorants and room air. We have found that we are able to complete 6 FMRI paradigms in each 1.5 hour imaging session (based on our previous 31 sessions). During the MR testing, patients will be monitored with pulse oxymetry in order to insure safety of the procedure and the scanner. The subjects will have a handball device in the MR magnet that they can squeeze in order to immediately stop the scans and be removed from the magnet should they experience any discomfort during the FMRI session.

Before and after each scan, we will fill out a questionnaire (Appendix 3) as to the quality of the stimulants used and the subject's experience with them through the olfactometer. We will therefore verify that our stimulants were correctly categorized as pleasant, neutral, or unpleasant.

**Paradigm designs:**

**Specific Aim #1:** All 240 normosmic subjects defined in the table above will perform the paradigms listed below. From their data individual and group FMRI maps will be created that allow for inrasubject and intersubject, intragroup and intergroup comparisons.

**Specific Aim #2:** In order to study the effects of unilateral versus bilateral nasal stimulation, olfactory nerve versus trigeminal stimulants, and pleasant versus aversive stimulants each subject will undergo the following FMRI tests:
1) Unilateral versus bilateral nasal stimulation

For all tests we will first instruct the patient on partial velopharyngeal closure techniques that allow passive influx of the odorants into the nasal cavity without sniffing. The olfactometer's nosepiece can be converted from having bilateral nasal insertions to unilateral nasal insertions. We plan to perform scans with right versus left versus bilateral nostril stimulation using eugenol (or the neutral olfactory nerve odorant substitute) as the stimulant. We have chosen eugenol because it is typically rated as neutral on pleasantness ratings and because it is rarely detected by anosmics and by "trigeminal focus groups" [10]. The "neutrality" of eugenol will be verified by scores between 4-6 on a 10 point rating system (from 1 "extremely unpleasant" to 10 "extremely pleasant") administered to the patient before entering the scanner. Eucalyptol or amylbutyrate will be substitute neutral odorants if eugenol elicits strong reactions one way or another since they have typically been rated as neutral in a previous study of over 429 subjects [106, 107].

The neutral olfactory stimulant will be varied with room air at 30 second intervals. As described above, there will be a 1 second influx of the odorant every 3 seconds (at times 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28 seconds) of the 30 second "on" period, followed by 30 seconds of the continuous room air "off" period. Right and left sides will be tested with the exact same stimulation sequence and compared with the bilateral stimulation results. We will control for air flow effects by using an air flow of 4 liters/minute bilaterally and 2 liters/minute unilaterally.

Before the subject enters the magnet we will perform acoustic rhinometry to assess for gross differences in the nasal volume between the 2 sides of the nose. All participants will be evaluated using acoustic rhinometry (Eccovision", Hood Laboratories Inc., Pembroke, MA). Lateralized measurements will establish both the minimal cross-sectional area (MCSA) of the nasal cavity and the volume of the nasal cavity over a length of 3.5 cm. Only subjects with symmetrical nasal cavities (ratio between left:right nasal volume or MCSA, respectively, between 70 and 130 %) and a minimum MCSA >0.2 cm2 will enter the study. In this way we can exclude the possibility that a widely disparate nasal volume will affect our unilateral FMRI results. These measurements take approximately 5 min. The MCSA data may be used later to see if there is an effect on unilateral FMRI results.

2) Olfactory nerve vs trigeminal nerve stimulation

The odors will be administered through a nosepiece with bilateral nasal insertions. We will use a neutral olfactory nerve stimulant and a selective trigeminal stimulant that is rated neutrally. Eugenol, coumarin or decanoic acid are options for relatively selective olfactory nerve stimulants since they are rarely detected by anosmics and by "trigeminal focus groups" [10]. Menthol was detected by 15 of 15 anosmic individuals but usually is rated neutrally by subjects and will be the "default" selective trigeminal stimulant [10] we intend to use. The "neutrality" of these odorants will be verified by scores between 4-6 on a 10 point rating system (from 1 "extremely unpleasant" to 10 "extremely pleasant") administered to the patient before entering the scanner. Methanol or carbon dioxide could be alternative neutral trigeminal nerve stimulants [10]. Recently, Laska et al have used menthol and cineol as trigeminal stimulants for congenitally anosmic patients so there is precedence for our selections of stimulants [50].

3) Pleasant versus unpleasant odor stimulation

We plan to offer phenyl ethyl alcohol as the default "pleasant" odorant and hydrogen sulfide as an aversive odorant for our tests. However if the PEA does not score above ≥7 out of 10 on a pleasantness scale and the hydrogen sulfide does not score ≤3 out of 10, we will offer other odorants such as geraniol or citral (for pleasant) and terpineol for aversive. Our goal is to keep both of these odorants as selective for the olfactory nerve as possible. PEA and geraniol are detected by less than 15% of anosmic individuals with very low intensity ratings [10]. Hydrogen sulfide and terpineol at low concentrations are also detected by less than a third of anosmic individuals and are rated as low in intensity [10].

Each of the odorants described above will be varied with room air at 30 second intervals. During the 30 second on period, there will be a 1 second influx of the odorant every 3 seconds (at times 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28 seconds of the 30 second on period). This will be followed by 30 seconds of the continuous room air "off" period.

Given that we can perform 6 paradigms per 1.5 hours of scanning, our total scanning protocol will include:

1) Unilateral vs bilateral: 3 paradigms (one for left nostril stimulation, one for right nostril stimulation, and one for bilateral stimulation; by using the olfactory nerve odorant from these series in the next experiment we will have our comparison for trigeminal activation)
2) Olfactory nerve vs trigeminal nerve: 1 paradigm using bilateral nasal stimulation for trigeminal nerve (the bilateral olfactory nerve stimulant is included above)

3) Pleasant versus unpleasant: 2 paradigms using bilateral nasal stimulation

**Specific Aim 3:** The patients with post-traumatic hyposmia, and schizophrenia will undergo all of the paradigms listed above. However, patients with congenital anosmia will also undergo a sniffing protocol to be described below. Since some investigators have suggested that it is the sniff that activates the entorhinal cortex and not the odorants, we plan to use the congenital anosmic subjects as the subject group which can eliminate the olfactory component of the sniff. In this way we can evaluate the effect of air flow into the nose of an odorant without having the "smell" input to the brain. This will require one additional paradigm that will substitute for the coronal scan through the olfactory bulbs and tracts, since the subjects that we will be studying don't have olfactory bulbs or tracts.

4) Sniffing versus passive stimulation

We will train the subjects on sniffing techniques that do not cause head movement in the magnet. We will then give a visual cue through a light source to "sniff" every 6 seconds for 30 seconds (time 2, 8, 14, 20, and 26 seconds of the 30 second "on" period). At the same time, an odorant (eugenol) will presented every 3 seconds (at times 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28 seconds) to be coordinated with sniffing every 6 seconds (time 2, 8, 14, 20, and 26 seconds) during the 30 second "on" period. We have found that a one second delay from odor delivery to sniffing will ensure that the subject gets the full effect of the odorant. The "on period" will be alternated with 30 seconds of the continuous room air "off" non-sniffing. These results will be compared with those in paradigm 2 where eugenol (or a substitute olfactory nerve odorant) was administered passively without sniffing.

We plan to train the subjects on the size and duration of the sniff in a session before being placed in the magnet. Using a manometer that measures pressure and airflow, we will teach each subject how to sniff in the magnet to provide 2 second duration sniffs with similar strength. The method of sniffing will be retaught to the patient right before entering the magnet to ensure that the sniff mechanism is uniform across all subjects. The 2 second inhale sniff will be alternated with 4 seconds of exhale and rest providing a physiologic respiratory rate of 10 breaths per minute. We will signal the cues to inhale and exhale via a light source that the subject will be able to see inside the magnet. The light source and the breathing rate will be maintained through both on and off periods to eliminate these effects on the FMRI subtraction maps. A verbal cue will be given at the end of each 30 second "on" interval to tell the patient to stop sniffing.

One of the strengths of the FMRI program at the University of Pennsylvania is the availability of a 4.0 Tesla magnet which provides improved signal to noise for FMRI experiments. Thus far our experience is greater with 1.5 Tesla (22 subjects) than 4.0 Tesla (7 subjects), however we plan to reanalyze the data once we have 20 subjects who have had 4.0 T studies. If the signal to noise and statistical significance of activation is improved at 4.0 Tesla without incurring artifacts at the skull base that affect visualization of the necessary structures for olfactory analysis (orbitofrontal, cerebellar, entorhinal, piriform regions etc.) then we will schedule all studies on the 4.0 Tesla magnet. In the initial months of the study, however, we will perform the same paradigms on the same patients at both 1.5 T and 4.0 T.

Summary of scans performed: 1) Sagittal T1W (1.5 minutes), 2) Axial T1W (7.0 minutes), 3) Coronal T1W (6.0 minutes) 4) Axial FLAIR volumetric scan (3 minutes), 5) Distortion correction (2 minutes), 6-11) Axial EPI FMRI (36 minutes). This means the actual total scan time will be 54.5 min in a 90 minute session.

Setting up the FMRI sequences, shimming the magnet, instructing and interviewing the patients between scans, and prescribing specific pulse sequences will lead to a full 90 minute session per patient for the FMRI scan time. In addition we plan to give patients a short break before the distortion correction scan. We will take them outside the magnet for instructions and personal contact. This tends to relieve some anxiety and/or feelings of claustrophobia and encourages subjects to complete their entire package of scans. All 31 of our previous subjects have completed all FMRI runs without feeling the need to be removed. Since lack of movement is imperative during FMRI scans, we will not routinely withdraw the patient from the scanner after the distortion correction.

1. Data Analysis

*Overview of Statistical Analysis and Image Processing*
All image analyses will be performed using the conventions and protocols already developed at our institution for performing fMRI studies. The FMRI raw image data will be transferred via ETHERNET or DAT tape to a SUN Sparcstation for off-line reconstruction using in-house software developed in IDL (Research Systems Inc., Boulder Colorado). After reconstruction, functional statistical maps will be generated using SPM96. MR images will be analyzed using statistical parametric mapping [108, 109] which combines the approaches of the general linear model and the theory of gaussian fields to make statistical inferences about regional changes in signal. The echoplanar scans from each subject will be realigned to the structural MRI and motion-corrected using a least squares approach. The structural MRI and the realigned MR images will be spatially normalized into a standardized neuroanatomical space (Talairach and Tournoux) using a reference template. This reference template will have an associated Brodmann area template (also in Talairach space) for use in assigning activated voxels from the final SPM data read-out to specific Brodmann areas. MR images will be smoothed using an isotropic Gaussian kernel in order to conform the data to a Gaussian-fields model.

The fMRI data from the subjects will be analyzed with multivariate analyses of covariance (MANCOVA), in which global signal is treated as a covariate of no interest. This is an extension of the Analysis of Covariance model developed for activation scans by Friston et. al [110, 111]. Linear contrasts will test the effects of task conditions as well as the effects of handedness, gender, and age category. In order to adjust for whole brain volume, the whole brain volume will be determined, with the computed volumes incorporated into the SPM dataset, and included as a covariate in the Friston MANOVA's. SPMs will be obtained in which the value of each voxel is a t statistic (SPM(t)) or a Z score (SPM(Z)). Voxels are considered significant if their Z scores are significant at the 0.05 significance level after correction for multiple comparisons [111, 112]. The cortical areas which are hypothesized to be engaged during the olfactory tasks are the Brodmann areas defined in the specific aims, however we will search for other areas of the brain where activation may occur as we collect our data. The activation volume will be determined for these areas as the number of statistically significant voxels. The activation volume will be used as a measure of the degree of neuronal recruitment involved in the olfactory stimulation tasks.

Quantitating activation volumes will be a potent method for comparing volumes of activation. Regional brain volume analysis computer packages are available to determine regional volumes and we can use our extensive experience with windowing, thresholding, and outlining on the ISG Allegro Workstation to determine site specific volumes. Rather than assessing the degree of activation of the cortex, we are setting a threshold and analyzing the number of voxels in the brain that are activated upon our stimulation. In order to correct for whole brain volume which may be affected by age, head shape, and atrophy, each of the Friston MANCOVA models will include whole brain volume, computed external to SPM and incorporated into SPM, as a covariate.

The study will include 330 subjects. Multiple subjects will be recruited that possess each set of prespecified demographic characteristics. These demographic categories are age range, handedness and gender. For example 20 normal subjects will be right-handed, male, between 40 and 60 years of age. The analyses will include comparison of the degree of activation, as measured by the number of activated voxels in each brain region, adjusted for total brain volume, for groups of patients with different demographic characteristics. Thus, analyses need to be based on multi-subject designs. A single statistic image for each of group of subjects to be compared is created within SPM96. It is through the design matrix that these groupings of subjects is indicated. For example, when testing for differences in activation of left-handed and right-handed normal subjects, separate statistic images are created for left-handers and right-handers. These statistic images would then be compared to examine hypotheses involving differences in activation between left- and right-handers. Thus, the covariates representing these demographic factors, as well as whole brain volumes, will be incorporated into each of the design matrices as needed for each of the analyses described below, yielding a multiple subject study with varying conditions and covariates. The statistical image analyses will be done primarily within SPM96. However, to accommodate some of the analyses not easily done in this package, such as characterizing the demographic data and associated brain image values (eg. Activated voxels for various regions), the SPM multiple comparisons adjusted values for each of the brain regions under consideration will be output from SPM96 into IDL (Interactive Data Language, Research Systems, Inc. Boulder Colorado). The statistical images will be masked for Brodmann areas using the Brodmann area template map. Regional Brodmann area activation will be output into ascii text files for analysis in a statistical package. Such alternative analyses will be performed in S-plus (Statistical Sciences, Seattle Washington) or SAS, (SAS Institute, Cary, North Carolina).
Analyses for Proposed Aims - (performed by Warren Bilker, Core Statistician)

Analyses for Proposed Aim 1: In hypothesis 1 of this aim, the goal is to show that the primary sites of activation using olfactory nerve stimulants will be the orbitofrontal cortices, both anteroinferior temporal lobes, and the cerebellum. A Friston MANCOVA performed with the framework of SPM96 will first be fit to create the statistic images to be used to explore this hypothesis. The whole brain volume will be included as a covariate. All normal subjects will be included in the analysis. Linear contrasts will be used to test the effects of the task conditions. To test subhypothesis 1 of hypothesis 1, a statistic image will be determined for right-handed subjects only. Linear contrasts will be used to test for left and right hemisphere differences in the frontal and temporal lobe activations. An analogous approach will be used for subhypothesis 2 of hypothesis 1. To test hypothesis 2, separate statistic images will first be determined for male and female normal subjects, with whole brain volume included as a covariate in the Friston MANCOVA model. Linear contrasts will be used to test for differences in the level of activation in each of the olfactory eloquent areas. In hypothesis 3, separate statistic images will be determined for subjects with age ≤ 40 and for subjects with age > 60, with covariate adjustment for whole brain volume. Linear contrast will be used to test for differences in voxel activation in the primary olfaction regions of interest.

Analyses for Proposed Aim 2: To test hypothesis 1, separate images will be determined for subjects when there is left and right nostril stimulation, with whole brain volume included as a covariate in the Friston MANCOVA. Using the left nostril stimulation image, linear contrast will be used to test for differences in left and right entorhinal/piriform cortex voxel activation. An analogous analysis will be used for the right nostril activation. For hypothesis 2, separate images will be determined for subjects exposed to trigeminal and olfactory nerve stimulants. The voxel activation will be compared in the sensory and sensory associated regions and the entorhinal cortex locations using linear contrasts. For hypothesis 3, separate images will be determined for subjects exposed to unpleasant olfactory stimulants and pleasant ones. The voxel activation will be compared in the hippocampal, amygdaloid, and cingulate regions using linear contrasts. Linear contrasts will also be used to test for differences in the ratio of left to right orbitofrontal voxel activation as suggested in subhypothesis 1.

Analyses for Proposed Aim 3: For hypothesis 1, a statistical image will be determined for voxel activation based on congenital anosmia patients. Linear contrasts will be used to test for voxel activation in olfactory eloquent areas. For hypothesis 2, separate statistical images will be determined for congenital anosmics exposed to trigeminal stimulants and for age and gender matched controls exposed to trigeminal stimulants. Differences in the congenital anosmics and controls will be tested using linear contrasts. For hypothesis 3, separate statistical images will be determined for patients with post-traumatic hyposmia, congenital anosmics and for age and gender matched controls. Differences between voxel activation in patients with post-traumatic hyposmia and congenital anosmics and patients with post-traumatic hyposmia and controls will be tested using linear contrasts. For
subhypohesis 1 of hypothesis 3, differences in the temporal lobe and parietal activation between post-traumatic subjects and controls will be tested using linear contrasts. For subhypothesis 2, the analysis will be descriptive, based on observation of the voxel activations in each hemisphere relative to the location of the trauma. For hypothesis 4, separate statistical images will be determined for patients with schizophrenia and for age and gender matched controls. Differences between voxel activation in patients with schizophrenia controls will be tested using linear contrasts. Linear contrasts will also be used to test for differences in the ratio of left to right hemisphere frontal activation as proposed in subhypothesis 1.

Output:

Each subject will have 6 data sheets created for the 6 FMRI experiments performed (see Appendix 4). On this sheet will be demographic information for age, gender, and handedness as well as a designation if a normal control subject, congenital anosmic, post-traumatic hyposmic, or schizophrenic. The pleasantness grades for the stimulants used and UPSIT (unilateral and bilateral grades) scores will be recorded (Appendix 3). Following these data will be the FMRI output data with number of activated voxels, strength of activation (p value), and right or left Brodmann area specified. These data sheets will be submitted for statistical analysis and will be collated with the handedness survey, odorant survey, and psychophysical tests results for each subject. Dr. Warren Bilker, the biostatistician assigned to this project, will receive a copy of all data sheets and will analyze the data (see below). The whole brain volume will be assigned as a co-variate using SPM96. This volume will be listed on the data sheet as well.

Clinical Research Protocol

1. Recruitment through advertisements of Smell and Taste Center Registry

2. Phone interview with Research Coordinator (Rena Geckle) to determine handedness, age, gender, past history of any episodes that may adversely affect olfaction. (20 minutes)

3. Study explained and consent obtained by Rena Geckle and/or David Yousem (P.I.). Screen for contraindications for MRI, pregnancy. (10 minutes)

4. Psychophysical testing (supervised by Richard L. Doty through Core) (approximately 2 hours)
   a. Odor identification (UPSIT)
   b. Odor detection threshold
   c. Odor memory
   d. Hedonics testing
   e. Other (per Core protocol)

5. Olfactometer test for pleasantness rating to determine odors to be used for FMRI experiment (directed by Thomas Hummel, co-investigator) (5 minutes)

6. Acoustic rhinometry immediately prior to FMRI--assess airway volume (directed by Thomas Hummel, co-investigator) (10 minutes)

7. FMRI (supervised and attended by David Yousem, Joseph Maldjian, David Alsop with olfactometer run by Thomas Hummel) (1.5 hours)
   a. Unilateral versus bilateral stimulation with neutral olfactory nerve odorant
   b. Trigeminal versus olfactory nerve odorant
   c. Pleasant versus unpleasant odorant experiment
   d. Sniffing versus passive stimulation (congenital anosmics only)

8. Exit interview for pleasantness ratings (5 minutes)

9. Subject reimbursement
# Timeline of Data Accrual

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5. HUMAN SUBJECTS

1. Although sex and ethnic background will not be used as selection criteria for the study except to serve as normal controls, patients who have severe claustrophobia, pacemakers, metal implants, or a history of metal in the eyes, as well as pregnant patients will be excluded from evaluation since these are contraindications to MR scanning. A serum or urine pregnancy test will be offered to all women prior to the MR scan to determine if they could be pregnant. All individuals will be expected to undergo olfactory testing and nasal examination in the Smell and Taste Center prior to FMRI scanning.

Regarding inclusion of minorities: The subjects of this study will be selected by handedness, gender, and age-distribution. Ethnicity and race will not be controlled variables. Inclusion of minority subjects will be made within the confines of the design. We expect that a many of the subjects will be of African-American descent since the hospital is in a neighborhood which is predominantly Black and signs will be posted around that neighborhood to recruit subjects.

2. The MR scans will be performed as the source for research material. Films of the patients, volumetric analysis computer programs, and magnetic tapes will also be used. The results of standardized neuropsychological tests for schizophrenic patients and olfactory psychophysical tests for all subjects will also be utilized and stored.

3. The normal subjects will be recruited from advertisements in newspapers, postings around West Philadelphia, notices in newsletters, etc. The patients with congenital anosmia, post-traumatic hyposmia, and schizophrenia will be culled from the patient population referred to the UPSTC, Departments of Otorhinolaryngology: Head and Neck Surgery, Neurology, and Psychiatry at the University of Pennsylvania. Once the patient has been identified as falling within the potential inclusion group of this grant a description of FMRI and olfactory testing as well as the risk of the procedure will be explained to the patient by the RC. Informed consent will be obtained and co-signed. The consent form will be IRB approved.

Informed consent for the grant procedure will be reviewed the day of the FMRI scan without coercion. It will be made clear to the patient that participation is voluntary and that the patient’s care would not be affected by agreeing or not agreeing to participate in the MR scanning test. At any point during the MR scan the patient could refuse to participate further.

4. The olfactory and neuropsychological tests performed in this study are safe and have been administered to thousands of subjects of patients without incident.

The MRI imaging procedure is entirely safe and, with the exclusionary criteria adhered to, should pose absolutely no threat to the patient. Patients with severe claustrophobia may be agitated within the scanner but these patients also will be excluded from the evaluation.

5. Protection against risk: Risks of the patients and control subjects will be minimized by the appropriate selection of patients for MR scanning. At the initial evaluation of the patient and again before the MR scanning the exclusionary criteria for the MR scan will be reviewed with the patient in order to determine that they do not fit into any of these criteria. Patients will have a squeeze ball in the magnet to alert people for immediate care. All MR units are equipped with emergency care devices and a "crash cart" for medication and intervention. Patient confidentiality will be maintained at all levels including during data management of the volumetric analysis of the patients.

6. Risk benefit ratio: Because of the very small risk involved in olfactory testing, nasal examination, neuropsychological testing, and FMRI, the risk benefit ratio is dominated by very low risk. The benefit of the project consists in the understanding the pathophysiology of cortical and olfactory dysfunction in patients with diseases that affect the sense of smell. Individual patient’s benefit may be small.
Literature Cited:


6. VERTEBRATE ANIMALS: NOT APPLICABLE
7. CONSULTANTS/COLLABORATORS: NOT APPLICABLE
8. CONSORTIUM/ CONTRACTUAL ARRANGEMENTS: NOT APPLICABLE
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SUBTOTALS $106,574 $26,146 $132,720

**CONSULTANT COSTS**

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See next page.

$65,350

**SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD**

$219,870

**CONSORTIUM/CONTRACTUAL COSTS**

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**TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD**

$219,870
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**Year 04**

Neuropsychological Testing @$150/patient x 45 patients

$6,750

**Year 05**

Neuropsychological Testing @$150/patient x 45 patients

$6,750
## BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT

### DIRECT COSTS ONLY

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**TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD**

(Item 8a, Face Page)  $1,091,326

**JUSTIFICATION.** Follow the budget justification instructions exactly. Use continuation pages as needed.

* All categories have been incremented 4% for all succeeding years.

* NOTE: Salaries at $125,000 cap are not incremented 4%.
Budget:

David M. Yousem, M.D. (Principal Investigator--35% effort)

Dr. Yousem is an Associate Professor in the Neuroradiology Section of the Department of Radiology with a joint appointment as an associate professor in the Otorhinolaryngology-Head and Neck Surgery Department. He currently is the radiologist supporting the Smell and Taste Center, the Head and Neck Cancer Center, and the Skull Base Surgery Center of the University of Pennsylvania Medical Center. He has a long-standing interest in the imaging of the olfactory system and has served as the principal neuroradiologist for the Smell and Taste Center for over 7 years. Dr. Yousem has been the principal investigator on grant # 5 PO1 DC 00161-15 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health and has in press or published over 10 papers in the field of imaging the olfactory system.

As principal investigator, Dr. Yousem will be responsible for overall coordination of the research. He will attend all FMRI sessions and will help analyze the data. He will register the data in Talairach space by fixed anatomic sites on the Sun Workstation. Dr. Yousem will perform the volumetric analyses of the whole brain volume required for SPM96. He will perform the group analyses and will be responsible for image generation and data storage.

Richard L. Doty, Ph.D. (5% effort /no money requested Co-Investigator--funded through Core)

Dr. Doty is the Director of the Smell and Taste Center at the UPMC and an Associate Professor in the Otorhinolaryngology-Head and Neck Surgery Department. He is acknowledged as one of the foremost authorities in psychophysical testing of the sense of smell in health and disease. Dr. Doty will coordinate the performance of the many olfactory tests in these patients. These will include the UPSIT, odor memory, and phenyl ethyl alcohol threshold testing. Dr. Doty will also supervise the performance of the minimental status examination and picture identification test on the patients. Through the Smell and Taste Center, organized by Dr. Doty, a brief nasal examination will be performed in order to exclude obstructive causes for olfactory loss.

Joseph Maldjian, M.D. (Co-Investigator--15% effort)

Dr. Maldjian is currently an assistant professor in the neuroradiology section at the UPMC. Dr. Maldjian will assist in the performance and interpretation of the FMRI studies. He will be principally involved in post-processing of the FMRI studies, storage of data, transferal of data, and writing programs to automate FMRI processing. Dr. Maldjian is proficient in IDL, SPM96, and UNIX command languages. He will perform the programming needed to process data and tailor it to the tasks specific to this grant.

Thomas Hummel, Ph.D. (Co-investigator--10% effort)

Dr. Hummel is on staff in the Smell and Taste Center and runs the olfactometer. He will be present at all FMRI sessions, performing the olfactory stimulation through the manipulations of the olfactometer. Dr. Hummel will be instrumental in the design of olfactory paradigms with respect to odorants used, unilateral or bilateral stimulation, airflow dynamics, and sniff testing).

Paul Moberg, Ph.D. (Co-Investigator--5% effort)

Dr. Moberg is a neuropsychologist in the Department of Psychiatry and Neurology. He will help design the olfactory stimulation studies for the magnet, recruit the schizophrenic patients, and perform the neuropsychological and olfactory tests on these patients. He will design tests to ensure that the normal subjects and other patient groups do not harbor occult schizophrenia.
David Alsop, Ph.D. (Co-investigator--5% effort)
Dr. Alsop has written the software for many of the echoplanar FMRI pulse sequences used in this study on both the 1.5 Tesla and 4.0 Tesla magnet. He will assist in adjusting protocols and enhancing FMRI image quality for the studies employed.

Rena Geckle: Neuroradiology Research Coordinator (100% effort--part time--50% total effort)
Rena Geckle has served as the neuroradiology research coordinator for the principal investigator since 1993. She has experience in dealing with all Smell and Taste Center staff and has develop a rapport with the patient base from which this study will recruit subjects. She will screen the subjects to ensure the proper "mix" of subjects are included in this study vis a vis handedness, gender, patient group, etc. Mrs. Geckle will schedule the patients for the clinical testing, olfactory testing, functional MRI scans, and the nasal examination. The neuroradiology research coordinator will organize the timely performance of these studies and develop a rapport with the patients so that completion of the study will be possible. The patient coordinator will also manage the reimbursement of patients for completion of all phases of the tests vis a vis the travel and meal allowances. If transportation is required, the patient coordinator will arrange for this and will see that the data as provided by the various investigators are stored in a permanent computer file.

Analysis of the data, correspondence to the patients regarding the results of their test, coordination of radiology reports and the patients films will be under the auspices of the neuroradiology research coordinator supervised by the P.I. Mrs. Geckle will also perform volumetric analyses of whole brain volumes, a technique she has performed frequently over the past 4 years with Dr. Yousem.

Data Processor: (50% effort): TBA
We have found that it is useful to have one individual assigned to perform the basics of data transfer and preliminary analysis. This person will retrieve the data tapes from each patient, load the data into the Sun Workstation, and assign file names to each patient and each patient's FMRI experiments. This individual will then perform the rudimentary SPM96 in which directory and localization information will be required. The data processor will also be taught to perform whole brain volumetric analyses. Dr. Yousem will then take the next step of normalization and registration and image generation.

Consultant fees:
A one time cost of $1000 is requested to provide seamless interfaces between Talairach, Brodmann, and MRI templates. Currently this is a manula process--we wish to automate this process with software written by the consultant.

Travel
Meeting costs for 2 investigators to present papers at the AChemS or Radiological Society of North America meeting per year is expected to run $2400.00.

Other Expenses
Current cost for performing an NIH sponsored MR scan is calculated at a rate of $350.00 per hour. We expect that it will take 2.0 hours to perform 1.5 Tesla and 4.0 Tesla FMRI scans on each subject. If we average 66 subjects per year for all 5 years to study 330 total patients, then the cost per year for subject scans will be 66 subjects X 2 hours X $350 per hour = $46,200.

Other patient costs include that for data tapes to archive studies, costs for filming of FMRI studies onto high quality color paper and film, costs for odorants etc are expected to run $100 per patient per year X 66 patients or $6600 per year.
Comprehensive olfactory testing of the patients is calculated at a cost of $200.00 per patient which includes all test materials and examiner time. This olfactory testing will include a nasal examination performed by a member of the Smell and Taste Center at the time of the olfactory testing. At $200/subject and 66 subjects per year the total cost per year for olfactory testing will be $13,200.

Neuropsychological testing is calculated at a cost of $150.00 per patient. These tests will be performed on the 30 patients with congenital anosmia, 30 patients with post-traumatic smell loss, and 30 patients with schizophrenia and will be performed in the 4th and 5th years of the grant at a rate of 45 per year. Therefore the additional expense in these years will be 45 subjects X $150 per subject = $6750.

Travel cost to and from the MRI center will be reimbursed and are expected to run $50.00 per patient for the year. We expect that the patients will require two trips to the MRI Center to complete their full olfactory stimulated FMRI protocol. The amount allotted would include the parking and meal costs for the visits to the Hospital during which time clinical testing, olfactory testing, and functional MRI examinations will be performed. An incentive to complete the testing must be included at a rate of $100.00 per patient. These costs would amount to 66 subjects X $150 per subject per year = $9900.

Computer costs include allocations for an Iomega Jaz Drive (1 gigabyte capacity removable disks) for data storage. A Sun UltraSparc workstation external hard drive and monitor with 4 gigabyte of memory for data analysis of the FMRI studies will cost $12,000. The software and license to run Interactive Data Language (IDL), the processing language for FMRI, costs $3000. MATLAB, to run the SPM96 program also costs $3000. Telephone, fax, mailing, paper and Xerox costs will run approximately $1000.00 per year as well.
BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2. Photocopy this page or follow this format for each person.

NAME
DAVID M. YOUSEM, M.D.

POSITION TITLE
ASSOCIATE PROFESSOR

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Michigan, Ann Arbor, MI</td>
<td>B.S.</td>
<td>1977-80</td>
<td>Biomed. Sci.</td>
</tr>
<tr>
<td>University of Michigan, Ann Arbor, MI</td>
<td>M.D.</td>
<td>1979-83</td>
<td>Medicine</td>
</tr>
<tr>
<td>Union Memorial Hospital, Baltimore, MD</td>
<td>Intern</td>
<td>1983-1984</td>
<td>Medicine</td>
</tr>
<tr>
<td>Johns Hopkins Hospital, Baltimore, MD</td>
<td>Resident</td>
<td>1984-1988</td>
<td>Radiology</td>
</tr>
<tr>
<td>Hospital of the University of Pennsylvania, Philadelphia, PA</td>
<td>Fellow</td>
<td>1988-1990</td>
<td>Neuroradiology</td>
</tr>
</tbody>
</table>

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience:
1983-1984 Intern, Internal Medicine, Union Memorial Hospital, Baltimore, MD.
1984-1987 Resident, Diagnostic Radiology, Johns Hopkins Hospital, Baltimore, MD
1988-1990 Fellow, Neuroradiology, Hospital of the University of Pennsylvania, Philadelphia, PA.
1990-1993 Assistant Professor, Department of Radiology, Neuroradiology Section, HUP, Phila, PA.
July 1993-pres. Associate Professor, Department of Radiology, Neuroradiology Section, Department of Otorhinolaryngology: Head and Neck Surgery, HUP.

Editorial Positions:
1991-present Appointment to Editorial Board of Radiology, Associate Editor
1991-present Reviewer for American Journal of Rhinology, Ad hoc reviewer for Journal of Neurosurgery
Ad hoc reviewer for Journal of Computed Assisted Tomography, Ad hoc reviewer for American Journal of Neuroradiology, Radiology

Honors and Awards:
1977-1981 Branstrom Prize for Academic Excellence; Freshman Scholar; James B. Angell Scholar;
Univ. of Mich. (4.0 GPA)--3 years; Class Honors--4 years; National Dean’s List; Phi Beta Kappa Society;
Undergrad. Graduation Summa Cum Laude (GPA 3.92)
1979-1983 Junior Alpha Omega Alpha, Senior Alpha Omega Alpha, Graduation with Highest Distinction
University of Michigan Medical School
1986-1987 Chief Resident in Radiology at the Johns Hopkins Hospital
1990 RSNA Research and Education Fund Grant Recipient Toshiba Medical Systems sponsor
1992,93,94,95 Invitation to RSNA Leadership Reception in recognition of service to RSNA
1992 Certificate of Merit for Scientific Exhibit at RSNA, Young BJ, Yousem DM, MR of the
Pterygopalatine Fossa (11-019)
1993,94,95 Editor’s Certificate of Recognition, RADIOGRAPHICS

Publications


Loevner LA, Yousem DM. The overlooked occipital condyle: a missed case treasure trove; Radiographics 1997;17:1111-1121.


Loevner LA, Yousem DM, Montone KT et al. MR of pre-epiglottic fat invasion. AJR (in press).


BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2. Photocopy this page or follow this format for each person.

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<tr>
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<th>POSITION TITLE</th>
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<tr>
<td>JOSEPH A. MALDJIAN, M.D.</td>
<td>ASSISTANT PROFESSOR</td>
</tr>
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EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<tr>
<td>UMDNJ- New Jersey Medical School</td>
<td>M.D.</td>
<td>1984-1988</td>
<td>Medicine</td>
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</table>

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience
7/1/97-present Assistant Professor of Radiology, University of Pennsylvania Medical Center, Department of Radiology, Philadelphia, PA.
7/95 - 6/97 Assistant Professor of Clinical Radiology, Department of Radiology, UMDNJ-New Jersey Medical School.

Hospital and Administrative Appointments
7/95 - 6/97 Director, Functional Imaging Laboratory (UMDNJ)
7/95 - 6/97 Attending Staff, Department of Radiology, VA Hospital, East Orange, NJ
9/96 - 6/97 Attending Staff, Department of Radiology, Bergen Pines Hospital

Specialty Certification
1993 American Board of Radiology
1995 Certificate of Added Qualification, Neuroradiology, ABR

Honors and Awards
1984 Magna Cum Laude, Biochemistry, Princeton University
1992-1993 Chief Resident, Department of Radiology

Publications


Holodny AI, Arutiunov NV, Kornienko WN, Gonzales R, Vairis C, Petriein AV, Maldjian JA. Aqueductal stenosis leading to herniation of the frontal horn of the lateral ventricle into the frontal sinus. JCAT (accepted Feb, 1997).

Maldjian JA, Schuler M, Liu WC, Mun IK, Hirschorn D, Murthy R, Carmel Pk, Kalnin A. Intraoperative Functional MRI using a real-time neurosurgical navigation system. JCAT (accepted June, 1997).
BIographical Sketch

Give the following information for all new key personnel, consultants, and collaborators.
Copy this page for each person.

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
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<tr>
<td>Paul J. Moberg</td>
<td>Assistant Professor</td>
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EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<tr>
<td>Augsburg College, Minneapolis, MN</td>
<td>B.A.</td>
<td>1982</td>
<td>Psychology</td>
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<tr>
<td>Loyola College, Baltimore, MD</td>
<td>M.A.</td>
<td>1985</td>
<td>Clin. Psychology</td>
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<tr>
<td>UHS/The Chicago Medical School, Chicago, IL</td>
<td>Ph.D.</td>
<td>1990</td>
<td>Clin. Psychology</td>
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<tr>
<td>University of Florida, Gainesville, FL</td>
<td>Post Doc</td>
<td>1991</td>
<td>Neuropsychology</td>
</tr>
</tbody>
</table>

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Research And Professional Experience:

1991-         Assistant Professor of NeuroPsychology, Department of Psychiatry, University of Pennsylvania

1991-         Director of Clinical Services, Neuropsychology Service, Brain Behavior Laboratory
Department of Psychiatry, University of Pennsylvania

1991-         Research and Clinical Associate, Smell and Taste Center, Department of Otolaryngology/Head and Neck Surgery, University of Pennsylvania

1989-90       Predoctoral Internship, Department of Clinical And Health Psychology,
J. Hillis Miller Health Center, University of Florida

1988-89       Psychogeriatric Research Coordinator, Department of Psychiatry,
Johnston R. Bowman Health Center for the Elderly, Rush-Presbyterian-St.Luke’s Medical Center

1982-85       Research Associate, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins Univ. Hospital

PUBLICATIONS


neuroleptic-naive and neuroleptic-withdrawn schizophrenic patients and their siblings. *Journal of Abnormal Psychology.*


BIOGRAPHICAL SKETCH

NAME

Thomas Hummel, M.D., Ph.D.

POSITION TITLE

Research Assistant Professor

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<tr>
<td>University of Erlangen-Nürnberg, Germany</td>
<td>med. registration</td>
<td>1980-86</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of Erlangen-Nürnberg, Germany</td>
<td>M.D.</td>
<td>1984-87</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>University of Erlangen-Nürnberg, Germany</td>
<td>Pharmacologist</td>
<td>1987-95</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>University of Iowa, Iowa City, USA</td>
<td>Fellow</td>
<td>1992-93</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>University of Erlangen-Nürnberg, Germany</td>
<td>Fellow</td>
<td>1993-96</td>
<td>Pharmacology / Physiology</td>
</tr>
<tr>
<td>University of Erlangen-Nürnberg, Germany</td>
<td>Ph.D. (Stabilization)</td>
<td>1990-96</td>
<td>Pharmacology</td>
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<tr>
<td>University of Pennsylvania, Philadelphia, USA</td>
<td>Ass. Prof.</td>
<td>1996-pres.</td>
<td>Otorhinolaryngology</td>
</tr>
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</table>

Professional Experience:

1986-1992 Joint appointment, Dept. of Pharmacology, Univ. of Erlangen-Nürnberg, Germany
1992-1993 Fellow, Dept. of Pharmacology, Univ. of Iowa City, Iowa, USA
1993-1996 Joint appointment, Dept. of Pharmacology, Univ. of Erlangen-Nürnberg, Germany
8/1996 - pres. Assistant Professor, Dept. of Otorhinolaryngology, Univ. of Pennsylvania, Philadelphia

Editorial Activity:

1995-pres. Editorial Board, Chemical Senses

Honors and Awards:

1992 Feodor Lynen Fellowship Award (DM 36,000)
1996 Takasago Award for excellence in Chemoreception Sciences (US $ 5,000)

Grants:


Bibliography:

Biographical Sketch

Thomas Hummel, M.D., Ph.D.

Page 2


Kobal G, Hummel T, Van Toller S (1992) Differences in chemosensory evoked potentials to olfactory and somatosensory chemical stimuli presented to left and right nostrils. Chem Senses 17:233-244


BIODIVERSITY

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME
Warren Bruce Bilker

POSITION TITLE
Assistant Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania, School of Medicine

EDUCATION/TRAINING (Begin with Baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>Temple University, Philadelphia, PA</td>
<td>B.A.</td>
<td>1981</td>
<td>Mathematics</td>
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<tr>
<td>Temple University, Philadelphia, PA</td>
<td>M.S.</td>
<td>1984</td>
<td>Statistics</td>
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<tr>
<td>Johns Hopkins University, Baltimore, MD</td>
<td>Ph.D.</td>
<td>1992</td>
<td>Biostatistics</td>
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RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience:

August 1982 and May 1983 - June 1983

Adjunct Lecturer, Temple University, Department of Statistics, Philadelphia, Pennsylvania

April 1983 - August 1983

Statistician and Programmer, Temple University, Department of Statistics, Philadelphia, Pennsylvania

January 1984 - July 1984

Assistant Analyst I, New Jersey State Department of Health, Trenton, New Jersey

July 1985 - December 1985

Statistician and Programmer, Department of Biostatistics, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

January 1986 - August 1986

Statistician and Programmer, Department of Neurosciences, Johns Hopkins Medical School, Baltimore, Maryland

January 1987 - August 1988

Statistician and Programmer, Department of Mental Hygiene, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

December 1986 - September 1991

Statistician and Programmer, Department of Hospital Epidemiology, Johns Hopkins Hospital, Baltimore, Maryland

September 1989 - September 1991

Statistician and Programmer, Department of Mental Hygiene, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

October 1991 - October 1992

Instructor, Department of Health Policy and Management, Johns Hopkins University School of Hygiene and Public Health and Hospital Biostatistician, Johns Hopkins Hospital Research Assistant Professor of Biostatistics in Medicine, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania

November 1992 - June 1995

Research Assistant Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania

July 1995 - present

Assistant Professor of Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania

Publications (February 1997)


Warren B. Bilker

Publications (February 1997) (continued)


Medoff-Cooper, B., Verklin, T., Myrns, N., Bilker, W., Kaplan, J., State and Suckling Behavior in 1 and 2 Day Old Infants, 1995, Submitted.


**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed on Form Page 2. Photocopy this page or follow this format for each person.

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard L. Doty</td>
<td>Director, Smell &amp; Taste Center</td>
</tr>
</tbody>
</table>

**EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).**

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado State Univ. Ft. Collins</td>
<td>B.S.</td>
<td>1966</td>
<td>Psychol &amp; Biology</td>
</tr>
<tr>
<td>California State Univ, San Jose; NASA Moffett Field, CA</td>
<td>M.A.</td>
<td>1968</td>
<td>Psychophysics</td>
</tr>
<tr>
<td>Michigan State University, Lansing</td>
<td>Ph.D.</td>
<td>1971</td>
<td>Comp &amp; Physiol Psych</td>
</tr>
<tr>
<td>University California, Berkeley</td>
<td>Postdoc</td>
<td>1973</td>
<td>Behav Endocrinology</td>
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**RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.**

**Professional Experience:**

1994 - 1996  Professor, Department of Otorhinolaryngology, School of Medicine, University of Pennsylvania, Philadelphia, PA.
1989 - 1994  Associate Professor, Department of Otorhinolaryngology, School of Medicine, University of Pennsylvania, Philadelphia, PA.
1980 - 1989  Assistant Professor, Department of Otorhinolaryngology, School of Medicine, University of Pennsylvania, Philadelphia, PA.
1980 - Present Director, Smell and Taste Center, University of Pennsylvania Medical Center, Philadelphia, PA.
1978 - 1979  Visiting Professor, Department of Psychology, University of Colorado.
1973 - 1978  Assistant Member, Associate Member, and Head, Human Olfaction Section, Monell Chemical Senses Center, Philadelphia, PA.

**Publications (from a total of 216):**


BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2. Photocopy this page or follow this format for each person.

NAME: JOSEPH A. MALDJIAN, M.D.

POSITION TITLE: ASSISTANT PROFESSOR

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
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<tr>
<td>UMDNJ- New Jersey Medical School</td>
<td>M.D.</td>
<td>1984-1988</td>
<td>Medicine</td>
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RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience

7/1/97-present  Assistant Professor of Radiology, University of Pennsylvania Medical Center, Department of Radiology, Philadelphia, PA.
7/95 - 6/97  Assistant Professor of Clinical Radiology, Department of Radiology, UMDNJ-New Jersey Medical School.

Hospital and Administrative Appointments

7/95 - 6/97  Director, Functional Imaging Laboratory (UMDNJ)
7/95 - 6/97  Attending Staff, Department of Radiology, VA Hospital, East Orange, NJ
9/96 - 6/97  Attending Staff, Department of Radiology, Bergen Pines Hospital

Specialty Certification

1993  American Board of Radiology
1995  Certificate of Added Qualification, Neuroradiology, ABR

Honors and Awards

1984  Magna Cum Laude, Biochemistry, Princeton University
1992-1993  Chief Resident, Department of Radiology

Publications


Holodny AI, Arutiunov NV, Kornienko WN, Gonzales R, Vaicys C, Petraikin AV, Maldjian JA. Aqueductal stenosis leading to herniation of the frontal horn of the lateral ventricle into the frontal sinus. JCAT (accepted Feb, 1997).
BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME
Rena J. Geckle

POSITION TITLE
Research Coordinator

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR CONFERRED</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Indiana University, Indiana, IN</td>
<td>A.S.</td>
<td>1978</td>
<td>Radiologic Technology</td>
</tr>
</tbody>
</table>

Professional Experience:

1978-1982 Clinical/Research Technologist, CT Technologies, Wishard Memorial Hospital, Indiana University, Indianapolis, IN.

1982-1984 Clinical Research Manager, MR Applications, Indiana University Hospitals, Indianapolis, IN.

1984-1988 Director, Regulatory Affairs, Bruker Medical Instruments, Inc. Billerica, MA.

1993-1997 Research Coordinator, Hospital of the University of Pennsylvania, Philadelphia, PA.

Bibliography:


David M. Yousem, M.D. - Other Support

**PENDING**

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<td>&quot;Olfaction in Multiple Sclerosis&quot;</td>
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To clearly define the nature of the olfactory dysfunction present in MS.

No overlap.

**PENDING**

<table>
<thead>
<tr>
<th>Grant ID</th>
<th>Start Date</th>
<th>End Date</th>
<th>Percentage</th>
</tr>
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<tr>
<td>NIH</td>
<td>7/1/96</td>
<td>6/30/01</td>
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<td>Pl: Kumar, Anand</td>
<td>152,494</td>
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<tr>
<td>&quot;Late Life Depression: Neuroanatomic and Behavioral Substrates&quot;</td>
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To examine the neuroanatomic and cerebrovascular basis of late life major depression in subjects presenting at a geriatric primary care site.

**PENDING**

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<th>Percentage</th>
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<td>NIH-PAR-96-073</td>
<td>07/01/97</td>
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<td>Pl: Yousem, David</td>
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<tr>
<td>&quot;FMRI and PET of the Olfactory System&quot;</td>
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</table>

To determine the primary regions of the brain associated with odor detection, identification, discrimination, and odor memory using functional MRI and positron emission tomography (PET).

**ACTIVE**

<table>
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<th>Percentage</th>
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<tr>
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<td>Pl: Yousem, David</td>
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Project 2: MRI of Olfactory System
Request for continued support of the University of Pennsylvania Smell and Taste Center

No overlap

**ACTIVE**

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<tr>
<td>Res. Fndn.</td>
<td>CURRENT YR DIRECT 4250</td>
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</table>

"Odor Stimulated Functional MRI"
To identify patterns of brain activation that may predict progression to disease.

No overlap.
Other Support

Joseph A. Maldjian, M.D.

no other support
Other Support

Richard L. Doty, M.D.

ACTIVE

5P01 DC00161-15 (Doty) 12/1/93 - 11/30/98 95%
NIDCD $3,941,665
The major goal of this project is research on clinical disorders of taste and smell.

1R01 DC02974-01A1 9/30/96 - 5/31/02 25%
NIDCD $903,746.91
The major goal of this project provides support for the study on Multiple Sclerosis.

NIMH (Rachel Gur) 07/01/96 - 06/30/02 3%
$11,661,166
The major goal of this project provides support for the study on Schizophrenia.
Other Support

Paul J. Moberg, M.D.

Active

1 R01 DC02974-01A1 9/30/96 - 5/31/02 25%
NIH $903,746.91
The major goal of this project provides support for the study on Multiple Sclerosis.

5-R37-MH42191 01/01/95 - 12/31/99 50%
NIH $280,695
The major role of this project supports MRI studies in schizophrenia in a longitudinal design. It provides the funds to obtain MRI scans on all patients with schizophrenia and conduct neurobehavioral assessment.

5-P01-MH43880 08/01/96 - 07/31/01 6%
NIMH (Rachel Gur) $1,131,891

5-P01-DC00161-15 (Doty) 12/1/93 - 11/30/98 10%
NIDCD $3,941,665
The major goal of this project is research on clinical disorders of taste and smell.
Other Support

Rena J. Geckle

No other support
RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used at each performance site listed in Item 9, Face Page, and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Use "Other" to describe the facilities at any other performance sites listed in Item 9 on the Face Page and at sites for field studies. Use continuation pages if necessary. Include an explanation of any consortium/contractual arrangements with other organizations.

Laboratory:
There are currently over 30,000 square feet of laboratory space available in the MR Imaging Center of the Department of Radiology at the University of Pennsylvania. This laboratory space includes chemistry labs, electronic labs, animal surgical suites, seven NMR instruments and computer facilities.

Clinical:
Four clinical MR systems exist at the MR Imaging Center, approximately 1300 clinical MR examinations are performed each year in all disciplines of MRI.

Animal:

Computer:
We have five SUN workstations and a Silicone Graphics Indigo System currently available in the MR Imaging Center. There is a SPARK station in place, with an additional SPARK station awaiting delivery. In addition, there are at least twelve other SUN and SPARK workstations distributed between the various research groups that use the MR facility. Approximately 50 Macintosh desktop computers exist in the MR Imaging Center.

Office:

Other ( ):

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

There are five GE 1.5 Tesla MRI scanners, all of which are currently running 5X software, and four scanners currently possess multicoil capabilities. One of the five scanners has been equipped with ultrafast gradient technology to allow echo planar and other fast scan techniques to be performed. Three of the five scanners are considered clinical scanners, while one is a clinical research scanner, and the fifth is a purely research scanner.

There are two animal scanners, a 1.5 Tesla 30 cm bore system and a 4.7 Tesla 40 bore system within the MR Imaging Center. These systems are equipped both with a commercial imaging console and a home built prototype spectroscopy console. A 4 Tesla whole body system has been installed, and is operational. This system will be interfaced to a 5X GE Signa console and equipped with a high speed gradient system. There is another whole-body 1.5T MR system at the Metabolic Research Center for MR in vivo spectroscopy. This system is interfaced to a home-built spectroscopy console which offers remarkable flexibility.
Within the MRI Imaging Center there is an electronics laboratory with a large portion of its effort dedicated to surface coil design and construction. This laboratory includes large electronics, stock and testing equipment required for coil construction. We routinely design and construct coils for research and clinical applications in our MRI Imaging Center. Within the Department of Radiology there is a machine shop dedicated to machining equipment needed for both clinical and research applications in the department. This shop is routinely utilized to construct support apparatus for surface coils.

The University of Pennsylvania Health System, includes the Hospital of the University of Pennsylvania (HUP), the School of Medicine, and a network of more than 150 primary care physicians. HUP is a 725 bed clinical facility in Philadelphia employing 650 physicians. HUP admits 27,585 patients a year. Outpatient visits number 543,566 a year.

Computer Facilities: The University of Pennsylvania and the Department of Radiology maintain outstanding computing, networking and information systems. Each radiologist currently has a personal desk-top computer that is connected to the University-wide network (PennNET). The Department of Radiology has a very well developed local computer network, including a VAX mainframe and more that 20 UNL-based workstations for clinical and research use. For larger scale database analyses, CPU time is available for purchase from the University's extensive mainframe computing facilities, with VAX (8600 and 8700) and IBM mainframes. This computing environment provides a full range of computational features and services, including data management, tape processing, a wide variety of programming languages, statistical packages and technical consultation and is linked with the rest of the campus via PennNET. The Medical Informatics Group consists of 14 people who support various computing activities for the Department of Radiology. Various kinds of computing systems are used to support the Infrastructure including DEC VAX's various UNIX hosts, Apple Macintosh's and PC's. The group has several offices and a dedicated lab space for the development of computer applications. In addition the group has access to multiple clean rooms for the support of computer hardware systems. The Department also has a high speed (10Mbit) connection to the Internet.