fMRI Investigation of Central Olfactory Deficit in Early Alzheimer's Disease

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Introduction:

Impairments of olfactory discrimination and identification abilities are among the earliest signs of Alzheimer's disease (AD) [1-3]. Behavioral tests have demonstrated that olfactory deficits can be present very early in the disease process as clinically-detectable changes in cognition and memory begin to occur [3-4]. Early neuropathological changes occur in the entorhinal cortex and hippocampus which are involved in olfaction as well as in memory and other cognitive functions [5-6]. These findings raise the possibility that olfactory functional MRI (fMRI) measurement may provide a sensitive bioassay for early detection and evaluation of AD. The goal of this study was to investigate the pathophysiology of olfactory brain structures in early AD with olfactory fMRI.

Methods:

Human Subjects Twelve probable AD (mean age 74.3 ± 7.8 years; 5 male) and thirteen healthy age-matched controls (67.8 ± 9.8 years; 8 male) completed measures of depression, cognition, the University of Pennsylvania Smell Identification Test (UPSIT) [7], and received olfactory fMRI at 3.0T. Mean UPSIT scores were 22.2 ± 7.5 for AD and 34.1 ± 3.5 for controls (Table 1). AD participants met NINCDS-ADRDA criteria for early AD; controls had no history of otorhinolayrngeal, neurological or psychiatric conditions. The investigation was reviewed and approved by the Institutional Review Board of the Penn State University College of Medicine, and all volunteers provided written informed consent prior to participation.

Odorant Three concentrations of the odorant lavender (Quest International Fragrance Co.), made by diluting lavender in 1, 2-propanediol (Sigma), were used (0.10%, 0.32% and 1.0%). The odorant concentrations used were previously determined psychophysically outside of the scanner by an independent study with young normal subjects.

fMRI Study Protocol MRI images were acquired of the entire brain using echo planar imaging with a SENSE Factor of 2 on a Philips 3.0 T system (Integra, Philips Medical Instrument) with TR / TE / FA (repetition time / echo time / flip angle) = 3000 ms / 35 ms / 90°, field of view (FOV) = 230 × 230 × 120 mm^3, acquisition matrix = 80 × 80, 30 axial slices, slice thickness = 4 mm and number of repetitions = 177. During the execution of the fMRI paradigm, breathing instructions were given to the participants at a rate of 10 cycles / min (3 sec: "Breathe In" and 3 sec: "Breathe Out"). Odor presentation with a home built olfactometer [3] with a flow rate of 8 L / min was synchronized with image acquisition and began 1 sec before breathing in. Presented in increasing strength order, each lavender concentration was administered for 6 seconds, followed by a 45 second resting period of clean odorless air, with a total of three repetitions.

Data Processing and Analysis The fMRI data were normalized to the Montreal Neurological Institute brain template [9] and group analyses (student *t-tests*, ANOVA) on volume and location of olfactory activations were performed using SPM2 [10].

Results:

Region of Interest analyses identified significantly reduced activation with all odor intensities in the primary olfactory cortex (POC), insula and hippocampus in the AD group compared to controls ($p < 0.01$) (Table 1). Controls tended to habituate to odors of increasing intensity, while the AD group showed modest activations in the POC and insula only with the strongest intensity. The significant differences between groups in these three areas at the weakest intensity are shown in Figure 1.

	Lav 0.10%			Lav 0.32%			Lav 1.0%		
	POC	Hipp	Ins	POC	Hipp	Ins	POC	Hipp	Ins
AD (n = 12)	0	5	0	0	0	0	24	0	7
Con (n = 13)	525	380	418	42	2	42	48	0	4

Table 1: **Activation Cluster Size** (one-sample *t-tests* for each group at each strength with $p = 0.01$). Lav 0.10% = weakest lavender intensity; Lav 0.32% = middle lavender intensity; Lav 1.0% = strongest lavender intensity. POC = Primary Olfactory Cortex; Hipp = Hippocampus; Ins = Insula.

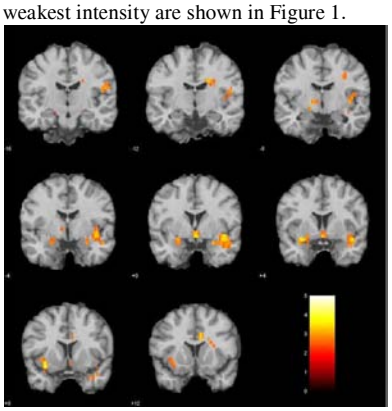

Figure 1: fMRI activation differences between control (n = 13) and AD (n = 12) groups for the odor lavender at intensity 0.10%. (two-sample t-test, $p < 0.01$, voxel cluster size = 10). Age-matched controls had significantly higher activation bilaterally in the POC, insula and hippocampus.

Discussion:

Olfactory fMRI responses to odor intensities in early AD are distinctively different from age-matched controls, with elevated thresholds and decreased volumes of activation. Although not anosmic, AD patients showed marked reduction of activation in the POC, hippocampus and insula. The long-term goal of this research is to understand the pathophysiology of olfactory deficits in the early AD brain. Olfactory stimulation requires minimal subject active participation and allows a direct bioassay in the brain structures that are most vulnerable to early AD pathology. These results demonstrated the feasibility of using olfactory fMRI to determine the critical functional-structural relationship of AD and as a biomarker for early detection of this neurodegenerative disease. Studies are currently underway to determine the sensitivity of olfactory fMRI as a bioassay for individuals at risk for early AD.

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