The Dynamics of Olfactory fMRI BOLD Response Differentiate Early AD and MCI from Healthy Controls

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Introduction:

Behavioral tests have demonstrated that olfactory deficits occur early in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), prior to clinically-detectable changes in cognition and memory [1-4]. Early neuropathological changes have been identified 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 Seven probable AD (mean age 76.29 ± 5.09 years; 1male and 6 female), eight probable MCI (70.25 ± 11.29 years; 4 male and 4 female), and eight healthy age-matched controls (73.13 ± 6.83 years; 4 male and 4 female) completed measures of depression, cognition, the University of Pennsylvania Smell Identification Test (UPSIT) [7], and received olfactory fMRI at 3.0T. AD participants met NINCDS-ADRDA criteria for early AD; MCI participants showed impaired memory that was isolated and not accompanied by other deficits to meet NINCDS-ADRDA criteria; controls had no history of otorhinolayrngeal, neurological or psychiatric conditions. Mean UPSIT scores were 22.6 ± 8.04 for AD, 25.38 ± 9.9 for MCI, and 34.5 ± 2.45 for controls. The investigation was reviewed and approved by our Institutional Review Board, and all volunteers provided written informed consent prior to participation.

Odor Stimulus Three concentrations of the odorant lavender was made by diluting it in 1, 2-propanediol to generate weak (0.10%), medium (0.32%), and strong (1.0%) concentrations that were previously determined from psychophysical study of healthy adults.

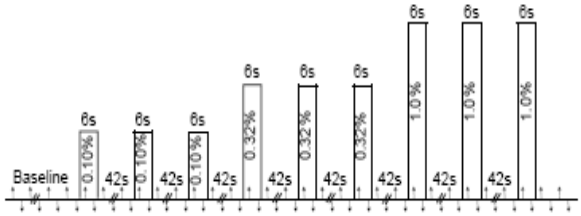

Figure 1: Odor intensity paradigm. Three odor concentrations were administered in order of increasing strength. Each odor stimulation was followed by a 42 second baseline of clean odorless air, with a total of three repetitions at each strength. During the execution of the fMRI paradigm, breathing instructions were given to the participants at a rate of 10 cycles / min (3 sec: "Breathe In" and 3 sec: "Breathe Out").

fMRI Study Protocol MR images were acquired of the entire brain using echo-planar imaging with a SENSE Factor of 2 on a Philips 3.0 T system (Achieva, 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. 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 inhalation (Fig. 1).

Data Processing and Analysis The fMRI data were normalized to the Montreal Neurological Institute brain template [8] and group analyses (student *t-tests*, ANOVA) on volume and location of olfactory activations were performed using SPM2 [9].

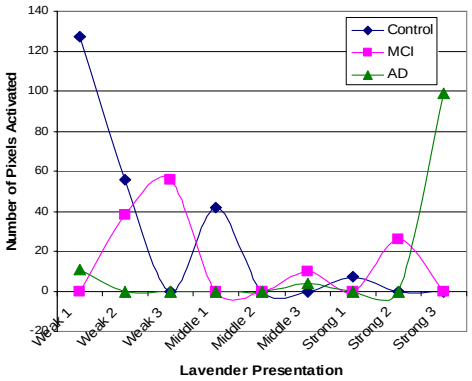

Figure 2: Number of pixels activated in the POC of Controls, MCI, and AD for each presentation of the weak scent (0.10%), middle scent (0.32%), and strong scent (1.0%). Region of Interest results (cluster size) listed for p=0.01 (one-sample t-test performed for each group at each lavender presentation).

Results:

As shown in Figures 2 and 3, a region of interest analysis of the primary olfactory cortex region (POC) revealed a unique dynamic pattern of BOLD signal with each odor presentation. Healthy controls showed the strongest POC activation to the first odor presentation (Weak 1). POC activity to Weak 2 and 3 then attenuated rapidly due to habituation. Subsequent stimulation with stronger odorants (Middle 1, 2 & 3 and Strong 1, 2 & 3 partially re-activated the POC on initial exposure and then repeated the attenuation pattern of habituation. The mild AD sample, in contrast, showed nearly a complete absence of such a dynamic pattern, generating only a very modest POC response to Weak 1 and activation with the last strong odor concentration exposure. The MCI group generated yet a different dynamic BOLD profile, with slow activity gain over repeated exposures, suggesting a priming effect, and habituation with increasing concentrations of the odors.

Discussion:

Olfactory fMRI responses to odor intensities in early AD are distinctively different from age-matched MCI and healthy control groups, with markedly decreased volumes of BOLD activity in the POC. Such functional pathophysiology is most likely due to the well-known neuropathological changes in the POC region. These findings provide neurobiological validation of the behavioral olfactory deficits identified in AD. The MCI group showed a uniquely different BOLD activation pattern in the POC from AD and age-matched control samples, with a slowed activation curve and virtually no habituation across repeated exposures within a concentration level. This difference could also be indicative of early neuropathological changes in the POC and post-lesion compensatory effects. These distinctive profiles of AD and MCI BOLD responses are promising since olfactory stimulation requires minimal active participation of subjects 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 certain critical function-structure relationships in AD and as a potential biomarker for early detection of this neurodegenerative disease and MCI.

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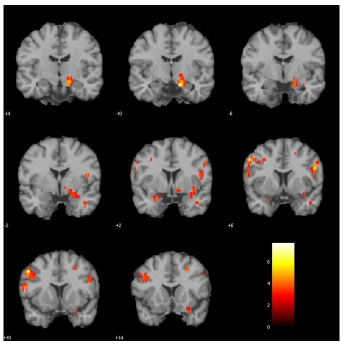

Figure 3: fMRI average activation for controls (n=8) for the odor lavender at intensity 0.10% during the first presentation (Weak 1). (one-sample t-test, $p < 0.01$, voxel size = 10). Activation is seen bilaterally in the POC, hippocampus, insula, and temporal poles.