Relationship of Functional Activation Deficit and Anatomical Atrophy in the Primary Olfactory Cortex and Hippocampus of Alzheimer’s Disease.

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**INTRODUCTION:**
Olfactory deficit is prevalent and can occur at very early stages in Alzheimer’s disease (AD) patients. The early pathological changes are known to occur in the medial temporal lobe, including the primary olfactory cortex (POC) and hippocampus. The observed local atrophy in these structures is thought to be associated with deficits in olfaction, memory and other cognitive functions [1]. The objective of this study is to investigate the direct relationship of atrophy in central olfactory structures to their functional deficit in AD by quantitatively determine the relationship of olfactory fMRI activation with local atrophy in the POC and hippocampus.

**METHOD:**
12 AD patients and twenty age-matched normal controls (NC) participated in this study. All AD and NC participants completed the University of Pennsylvania Smell Identification Test (UPSIT), which provided a standardized measure of olfactory perception abilities [2]. The anatomical and fMRI images were acquired using a 3T MRI scanner. The olfactory stimulation paradigm consisted of three concentrations (0.10%, 0.32% and 1.0%) of the odorant (lavender) administered sequentially with three repetitions for each concentration [3]. Each odor stimulation lasted for 6s, followed by 42s of baseline with odorless air. The hippocampus and POC were manually segmented. The areas outlined were saved as ROIs for subsequent fMRI activation calculations to obtain the activation voxels in those two local regions.

**RESULTS:**
The UPSIT scores were significantly different (21.17 ± 7.94 for AD and 30.85 ± 5.69 for NC). The volumes and activation voxels of POC and hippocampus are showed in Fig. 1. The AD group showed prominent atrophy in both the hippocampus and POC. Compared to NC group, the average volumes of the POC and hippocampus in the AD group were reduced by 39% and 44%, respectively. There was a high correlation between the atrophy of POC and hippocampus ($P<0.001$). Olfactory activations in the corresponding structures show a much greater reduction in AD: 98% in POC and 95% in hippocampus. The activation reduction and local atrophy in these two regions were significantly correlated ($P=0.008$ for POC and $P=0.033$ for hippocampus). Fig. 2 demonstrated olfactory fMRI activation difference in POC, hippocampus and insula between the two groups.

**CONCLUSION:**
The olfactory regions are preferentially involved in the early stages of AD. Postmortem studies have shown the neurofibrillary tangles appeared initially in the transentorhinal and entorhinal regions of AD brain and proceeded to hippocampus and other temporal lobe structures. The areas infiltrated by the neurofibrillary changes in the clinically silent and incipient stages overlap with the brain areas for olfaction [4]. Thus, in vivo measurement of olfactory structural and functional changes can be potentially used as an image marker for AD early detection. In this study, we determined the morphological and functional changes in the brain areas most susceptible to AD pathology. We revealed that the reduction of BOLD response due to the disease in POC and hippocampus was much greater than the structural changes in the corresponding areas. These results indicate that olfactory fMRI can be a more sensitive marker for detection and evaluation of neuropathological changes in AD.

Reference:

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