Primary Olfactory Cortex Involvement in Alzheimer's Disease: a functional and morphological MRI investigation

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Introduction: Alzheimer's disease (AD) is the most common form of dementia affecting 5.4 million individuals in the USA alone (1). During the time of clinical manifestations, the pathology has already progressed from the temporal lobe to the neocortex. Early diagnosis and understanding of the neural networks in AD are key in slowing the progression and unlocking a cure. Many studies have shown that the hippocampus, which is in the medial temporal lobe, decreases in size during the progression of AD and volumetric measurements provide excellent diagnostic assistance (2, 3). Other studies have also shown that the earliest markers of AD (amyloid beta plaques ($A\beta$) and neurofibrillary tangles (NFT)) are found first in regions that overlap with olfactory areas and that olfaction is affected in the early stages of AD and in Mild Cognitive Impaired (MCI) patients (4-7). Therefore in this study we hypothesized that the Primary Olfactory Cortex (POC) will show similar decrease in volume as the hippocampus in AD. We examined the POC and hippocampus during an olfactory fMRI paradigm to investigate the volumetric and activation differences between Cognitively Normal Controls (NC), MCI individuals, and AD patients.
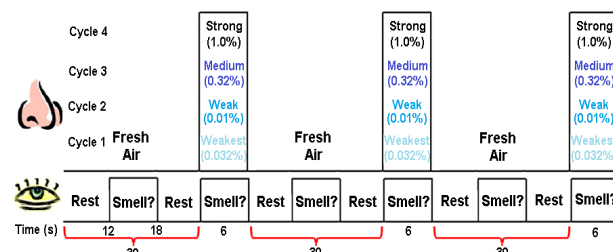

Fig 1. Olfactory fMRI paradigm. The above cycles 4x. The 4 lavender concentrations are presented 3x each. Every time "Smell?" appears on the screen the subject must respond yes if they smell lavender and no if they do not.

Methods: Cognitive tests and the University of Pennsylvania Smell Identification Test (UPSIT) were administered to all subjects. Then functional Magnetic Resonance Imaging (fMRI) was utilized to study the blood oxygen level dependent (BOLD) signal change in the POC and in the hippocampus. T_1 MPRAGE scans were collected for the anatomical underlay and EPI was acquired for the functional data on a 3 T Siemens Scanner. Lavender was used as the odorant. During the paradigm the subjects were asked to respond using a button press if they smelled lavender or if they did not smell lavender when the visual stimulus appeared on the screen (Fig. 1). The regions of interest (ROI), namely the POC and hippocampus, were manually segmented on T_1 images for each subject using FSLview and then SPM 8 was used to analyze the fMRI data. GraphPad Prism 6 was used for statistical analysis.

The subject population includes 23 Cognitively Normal Controls (mean age= 70.9 years, 14 females), 19 MCI (mean age= 73.2 years, 10 females), and 15 AD patients (mean age= 72.2 years, 9 females). There was no significant age or gender difference among the three groups.

Fig 2. Significant positive correlation between POC and hippocampus volumes. Black points are NC, red points are MCI, and green points are AD.

Results: Figure 2 shows a positive correlation between POC and hippocampus volumes. Indicated by the slope, the dynamic range of POC volumes is greater than that of the hippocampus. ANOVA testing ($p < 0.05$) showed that the means of the three groups were significantly different for both the POC and the hippocampus. Each individual's segmented structures were used to examine activation within the two structures. Figure 3 shows a positive correlation in activation between the POC and hippocampus. Interestingly, ANOVA analysis ($p < 0.05$) showed that the mean activated voxels of the three groups were significantly different for only the POC and did not reach significance for the hippocampus.

Discussion: Using neuroimaging techniques we have shown that the POC's involvement in AD is comparable to the hippocampus. Both the POC and the hippocampus are decreasing in volume in MCI patients and even more so in AD patients. Behavioral olfactory changes observed in patients may be due to this degeneration. We saw a positive correlation between UPSIT scores and the POC volume so that those with larger POCs performed better on the UPSIT. When examining the fMRI data, a positive correlation between the hippocampus and the POC was observed. Both of these areas showed activated voxels ($p < 0.05$) while the odor was being presented; however the POC had greater activated voxels and showed significant differences between the three groups. When looking at multiple comparisons analysis, the POC of NC had significantly greater activated voxels than the AD patients. The volume and activation correlation of these two ROIs shows that the POC is involved in AD. Literature also provides evidence for this involvement. AD pathology is seen in the olfactory areas at the earliest stages of the disease and smell loss is present in the early stages of AD and even in MCI patients (4-7). Therefore the POC is an important ROI to study in AD and MCI patients to learn more about changes that occur in the brain at the earliest stages. Future studies will include collecting more data specifically from MCI and AD patients, doing network analysis during the olfactory paradigm, and adding a pure olfactory paradigm without a visual prompt. We will also do a longitudinal study with our subjects.

Fig 3. Significant positive correlation between activated voxels in the POC and hippocampus. Black point are NC, red points are MCI, and green points are AD.

Conclusion: Utilizing morphological and functional MRI, our study shows that the POC is involved in early AD. The changes in the POC correlate with changes seen in the hippocampus in AD and MCI patients with a greater dynamic range. Our results show that morphology and olfactory fMRI of the POC has the potential to be a more sensitive early diagnostic marker for AD.

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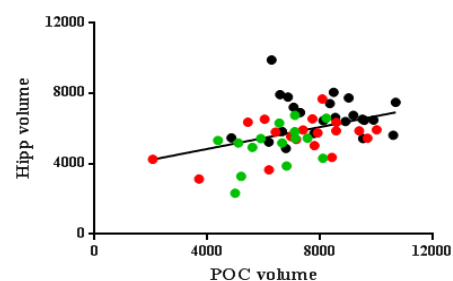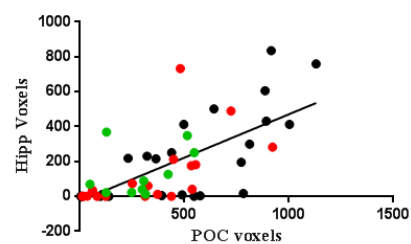[7] Murphy et al. Neurobiol Aging 11 (1990) 465-469