Functional connectivity of the primary olfactory cortex is decreased in Alzheimer's disease and mild cognitive impairment

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Introduction: Early diagnosis and understanding of the neural networks in Alzheimer's disease (AD) are key in slowing the progression and unlocking a cure. Studies have shown decreased functional connectivity of the default mode network in patients with AD and this has been suggested as an early marker for AD (2-3). Pathological studies have established that the AD pathology (amyloid beta plaques and neurofibrillary tangles) is first found in the 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 decreased functional connectivity in the AD and MCI subjects compared to cognitively normal controls (CN).

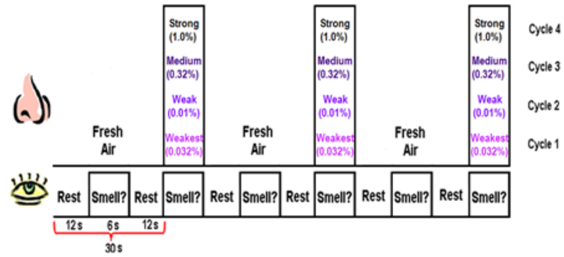

Fig 1. Olfactory fMRI paradigm. The above cycles 4x. The 4 lavender concentrations are presented 3x each. Every time "Smell?" appears on the screen the subject must respond yes if they smell lavender and no if they do not.

Methods: Cognitive tests and the University of Pennsylvania Smell Identification Test (UPSIT) were administered to all subjects. The subject population included 27 CN (mean age= 69.5 years, 15 females), 21 MCI (mean age= 73.2 years, 11 females), and 15 AD patients (mean age= 71.9 years, 10 females). There were no significant group differences in age, gender, or education. Then functional Magnetic Resonance Imaging (fMRI) was utilized to study the blood oxygen level dependent signal change in the POC. 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). DPARSFa and SPM8 were utilized to analyze the fMRI data and the seed regions (the left and right POC) were defined using coordinates based on previous manual segmentation of the POC. The seed was 6 mm in diameter. GraphPad Prism 6 was used for statistical analysis of the cognitive and UPSIT data.

Results: Figure 2 shows one sample t-tests of the areas that correlated with the left and right POC in each of the three groups (CN: $P < 0.001$, FWE; MCI and AD: $P < 0.05$, FWE) during the olfactory fMRI. ANOVA analysis ($P < 0.05$, FWE) showed significant group differences with the AD and MCI groups having significantly less functional connectivity of the left and right POC compared to the CN. There was decreased connectivity to the hippocampus, the reward network (caudate, putamen, nucleus accumbens), to the prefrontal cortex, and the default mode network for both the left and right POC. A greater functional connectivity was found in the left POC than the right POC in the CN. Decreased performance on the UPSIT was also observed for the AD and MCI groups compared to the CN. The UPSIT also showed decreased UPSIT scores for the AD group compared to the MCI subjects.

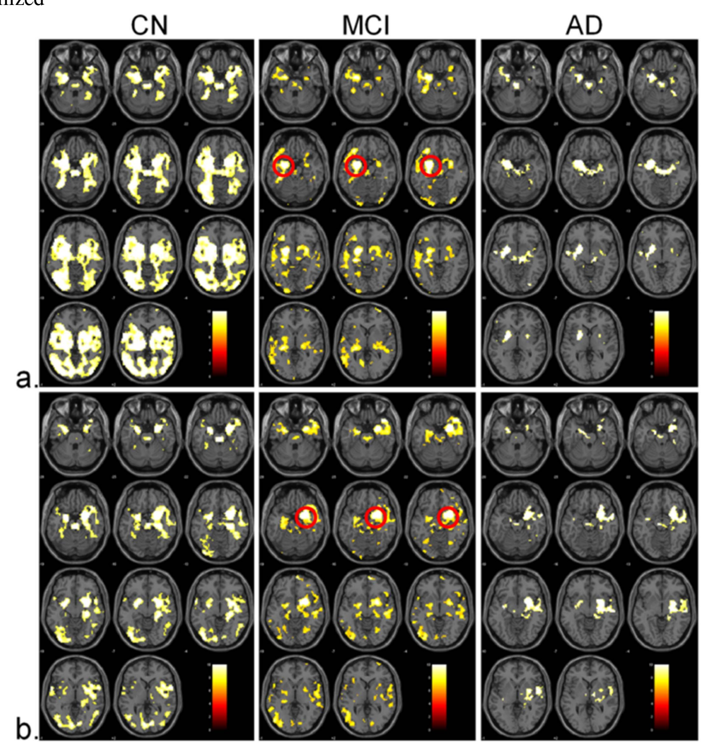

Fig. 2 Functional connectivity of the POC. One sample t-tests (CN: $P < 0.001$, FWE; MCI and AD: $P < 0.05$, FWE) are represented for each group. The left POC (2a) and the right POC (2b) show decreased functional connectivity of the POC to several brain regions including the hippocampus, caudate, putamen, nucleus accumbens, prefrontal cortex, and anterior cingulate cortex. The red circles approximate the position of the seed.

Discussion: Using functional connectivity analysis on our olfactory paradigm, we have shown that the POC has decreased functional connectivity to the reward network, default mode network, and the hippocampus in both the MCI and AD subjects. Interestingly, the MCI and AD subjects exhibit a prominent trend of loss of functional connectivity to the contralateral hemisphere. This supports the hypothesis that the loss of connectivity between the two hemispheres leads from cognitive decline to dementia in AD. Lateralization was also present in our subjects, the left POC displayed greater functional connectivity compared to the right POC. Our results suggest that the POC connects to many important functional networks involving memory, emotion, and cognition. Thus, AD pathology in the POC plays a central role for various functional deficits in addition to olfaction. Therefore, the POC is an important ROI to study in AD.

Conclusion: Utilizing olfactory fMRI, our study shows that the POC is involved in AD and most importantly in MCI. Our results also show that functional connectivity changes occur prior to cognitive and olfactory symptoms in MCI subjects. Therefore, the POC is an important region to study and together with fMRI may provide an early diagnostic marker.

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