Olfactory Neural Network Disruption in Alzheimer's disease (AD): A Functional Magnetic Resonance Imaging Study

Prasanna Karunanayaka[1], Megha Patel[1], Jian-Li Wang[1], Sarah Molitoris[1], Paul Eslinger[2], and Qing X Yang[1]

[1]*Radiology, Hershey Medical Center, Hershey, Pennsylvania, United States,* [2]*Neurology, Hershey Medical Center, Hershey, Pennsylvania, United States*

Introduction:

Patients with AD (including Mild Cognitive Impairment [MCI]) exhibit olfactory deficits before the appearance of overt memory loss. Thus, investigating olfactory-related networks has received considerable attention in recent years [1, 2]. In this study, we used Independent Component Analysis (ICA) to investigate the network structure (and the differences) that subserve olfactory processing in AD and NC [3, 4]. Using a four-strength smell-related fMRI paradigm, we revealed the underlying olfactory networks in aged normal (NC) normal and prominent alterations in Alzheimer's disease (AD).

Materials and Methods: 15 AD, 20 MCI and 31 NC (mean age 72 + 10 years) completed a four-strength olfactory fMRI paradigm at 3.0T [5]. Using an olfactometer (with a flow rate of 8 L/min and synchronized with image acquisition and visual cues), three rounds of each odorant concentration (6s per stimulation) were presented to the subject's nostrils sequentially, interleaved with a 30 sec period of odorless air between each stimulation.

The olfactory function of all participants was assessed using The University of Pennsylvania Smell Identification Test (UPSIT) [6]. The study had the Penn State College of Medicine IRB approval, and all volunteers provided written informed consent prior to taking part in the study.

MR images of the entire brain were acquired using EPI (with an acceleration factor of 2) on a Siemens Trio 3.0 T system with the following parameters: TR / TE / FA= 2000 ms / 30 ms / 90°; FOV = 220 × 220 mm^2; acquisition matrix= 80 × 80, 30 slices; slice thickness= 4 mm, and the number of repetitions= 234.

The group ICA analysis was based on FastICA algorithm and performed according to the methods outlined elsewhere [4]. We used individual IC time courses of respective groups as input to perform a second level correlation analysis.

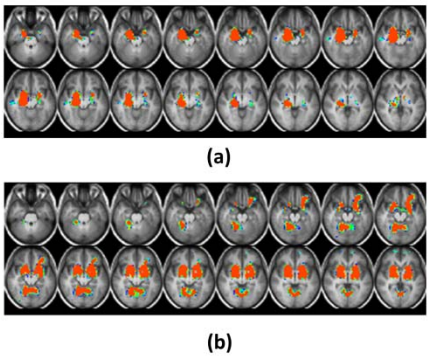

Figure 1. Two task-related ICA components found for the study group of 66 (AD, MCI and NC) participants performing the olfactory stimulation paradigm.

Results and Discussion: Figure 1 (left) shows two task-related group ICA maps that sub-serve the four-strength olfactory fMRI task in all three groups. These networks encompass: (a) Primary Olfactory Cortex (POC), amygdala, hippocampus, and insula; (b) striatum, putamen and POC. **Figure 2** shows the associated averaged time courses for these task-related networks. Presence of different cortical regions in the same ICA map implies a functional connectivity among these regions.

The correlation co-efficients of average time courses **IC (a)** for AD, MCI and NC (**Figure 2**) with the on-off task reference function were: 0.04 ($p > 0.05$), 0.21($p < 0.001$), 0.24($p < 0.001$). Similarly, for **IC (b)**, the respective correlation co-efficients for the three groups were: 0.14 ($p < 0.05$), 0.16, 0.86 ($p < 0.02$) and 0.37($p < 0.001$).

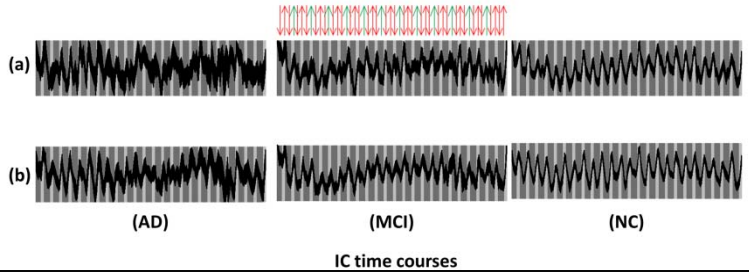

Figure 2. Associated IC time courses for the independent component maps shown in Fig. 1. ↓ = "Rest" + fresh air, ↑= "Smell ?" + fresh air, ↑= "Smell ?" + odor.

We further investigated the relationship between the task-relatedness of each network with respective UPSIT scores. In the MCI group, **IC (a)** showed a significant correlation between the task-relatedness and the respective UPSIT scores ($r=-0.54$, $p < 0.01$). **IC (b)** showed a correlation that can be identified with a trend. In other two groups (i.e., AD and NC) we did not find any such significant correlations.

Conclusion: ICA provided both the spatial and temporal information and is uniquely suitable for examining neural network disruptions by neurodegenerative diseases such as AD. One significant finding of this study is the identification of two networks (IC maps) presumed to be related to primary olfactory processing [5, 6]. Furthermore, we also found significant variability in these networks in the MCI group, reflecting the dynamic progression of the disease in this study cohort. Additionally, the temporal behavior of these sub-networks (**Figure 2**) clearly shows a disruption in the AD group. Unlike previous studies (where the emphasis was on few individual olfactory-related brain regions) our approach highlights the advantage of analyzing olfaction in terms of cognitive modules based on underlying network structure(s).

References: [1]. Gottfried J.A., *et al*.; Nat Rev Neurosci 2010; 11(9): 628-41. [2]. Yeshurun Y., *et al. Annu Rev Psychol. 2010; 61:219-41*. [3] Wen Li, et al; Brain 2010; 133: 2714–2726. [4]. Karunanayaka et al., NeuroImage 2010; 51:472-87; [5]. Kathleen M. Gates., *et al.*, NeuroImage 2011; 54(2):1151-58; [6]. Karunanayaka *et al.*; at ISMRM 2011. [6]. Doty R., *et al.;* Physiol Behav 1984; 32: 489-502;