Dynamic Behavior of BOLD Signal in Olfactory Neural Networks

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Introduction: It has been shown that the interplay of perception threshold, sensitivity, and habituation of the human olfactory system poses new challenges to the assumption of a linear BOLD response – profoundly impacting olfactory fMRI data acquisition and analysis methods for scientific and clinical applications [1-2]. Thus, the pattern of BOLD response during the time course of a standardized olfactory stimulation paradigm was investigated and characterized using group independent component analysis (ICA) due to its ability to reveal the underlying networks of the human brain subserving cognitive functions. [3].

Methods:

Human Subjects Ten healthy subjects (mean age 24.7 ± 1.8 years) completed two identical runs of an olfactory fMRI paradigm at 3.0T separated by approximately 5 minutes. Olfactory function of all participants was assessed using University of Pennsylvania Smell Identification Test (UPSIT) [4], and all participants scored within normal range, with an average score of 37.1 ± 1.5 out of 40. Investigation was approved by the Penn State College of Medicine IRB, and volunteers provided written informed consent prior to participation.

Odor Stimulus Paradigm Four concentrations of lavender odorant (Quest International Fragrance Co.) were prepared via dilutions in 1, 2-propanediol (Sigma) to generate weak (0.032%), medium (0.10%), strong (0.32%), and very strong (1.0%) concentrations.

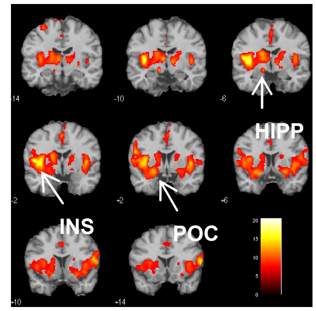

Figure 1: Average olfactory activation at all 4 lavender concentrations in healthy subjects (n=20, one-sample *t-test*, family-wise correction, $p<0.05$) [2].

fMRI Study Protocol MR images of entire brain were acquired using EPI with an acceleration factor of 2 on Siemens Trio 3.0T, TR/TE/FA 2000ms/30ms/90°, FOV 220×220×120mm^3, matrix 80×80, slices 30, slice thickness 4mm, and repetitions 234. Three presentations of each odorant concentration (6s/stimulation) were presented to subject's nostrils sequentially with 30s period of fresh air between each stimulation. Visual cues of "Rest" and "Smell?" were presented to subject, and odor was delivered during every other presentation of the cue "Smell?" (Fig. 3). Home-built olfactometer was used with flow rate 8L/min to synchronize odor delivery, image acquisition, and visual cues.

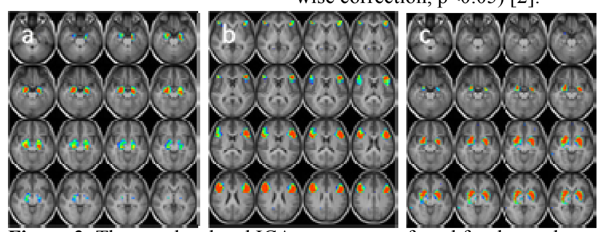

Figure 2: Three task-related ICA components found for the study group of 10 participants performing the olfactory stimulation paradigm.

Data Processing and Analysis fMRI data were normalized to Montreal Neurological Institute brain template [5] and group analyses (student *t-tests*, ANOVA) on volume and location of olfactory activations were performed with SPM5 [6]. Group ICA analysis was based on FastICA algorithm according to methods outlined in [3].

Results and Discussion: Fig. 1 shows significant bilateral activations in primary olfactory cortex (POC), hippocampus, insular cortex, and thalamus in two identical runs of an olfactory fMRI paradigm from random-effects GLM analysis. Group ICA method detected several additional olfactory circuits with unique time courses that were not detected in the standard GLM analysis: Fig. 2 (a) encompasses POC, amygdala, hippocampus, and insula; Fig. 2 (b) dorsolateral prefrontal cortex; Fig. 2 (c) striatum. Presence of different cortical regions in the same ICA map implies that the regions are functionally connected. Fig. 3 shows associated averaged time courses for 3 task-related networks shown in Fig. 2. The thickness captures the within-subject variability associated with these IC time courses. Time courses exhibit a task-related behavior, even for the condition where fresh air was delivered with "Smell?" cue. Our previous research [2] has shown that a 2nd run of an identical paradigm yields less activation in POC, indicating habituation. Therefore, habituation and an effect from the visual cue must be taken into consideration. ICA provides a basis to investigate such effects based on variability of time courses for each network.

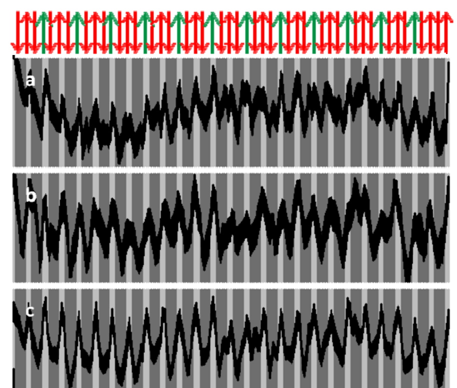

Figure 3: Associated IC time courses for the independent component maps shown in Fig. 2.
↓ = "Rest" + fresh air, ↑= "Smell?" + fresh air,
↑= "Smell?" + odor.

Conclusion: Group ICA method does not require a priori knowledge of hemodynamic response function (HRF), which may vary across subjects and paradigm conditions. Habituation effects in olfactory BOLD signal associated with IC time course is clearly demonstrated in Fig. 3 (a). A dynamic pattern under a given stimulation paradigm can thus be utilized to examine and detect functional changes in disease processes such as Alzheimer's disease and Parkinson's disease. Group ICA may also be combined with functional and effective connectivity analysis techniques to investigate causal structures of the olfactory system [3]. The results show the advantage of investigating olfactory fMRI paradigms in terms of underlying neural networks.

References: [1]. Yang Q.X., *et al.*, Magn Reson Med 2004; 52: 1418-1423. [2]. Weitekamp *et al.* at ISMRM 2010. [3]. Karunanayaka et al., NeuroImage 2010; 51:472-487. [4]. Doty R., *et al.* Physiol Behav 1984; 32: 489-502. [5]. Collins D.L., *et al.* IEEE Trans Med Imaging 1998; 17: 463-468. [6]. Friston K.J., *et al.* Human Brain Mapp 1994; 1: 153-171.