The Non-Linear Dynamic Characteristics of Olfactory BOLD ResponseΞ

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Introduction:

This study investigated the temporal BOLD response pattern in primary olfactory cortex (POC) and associated brain structures during the course of an olfactory stimulation paradigm. Results revealed striking nonlinear dynamic characteristics. The interplay of perception threshold, sensitivity, and habituation of the human olfactory system challenges the fundamental assumption of linearity in BOLD response, and therefore, profoundly impacts olfactory fMRI data acquisition/analysis and its clinical applications.

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 about 5 minutes. The olfactory function of all participants was assessed with The University of Pennsylvania Smell Identification Test (UPSIT) [1], and all participants scored within the normal range, with an average score of 37.1 ± 1.5 out of a total score of 40. The investigation was approved by the Penn State College of Medicine IRB, and all 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 that were previously determined from psychophysical study of a large cohort of healthy adults.

fMRI Study Protocol MR images of the entire brain were acquired using EPI with an acceleration factor of 2 on a Siemens trio 3.0 T system, TR / TE / FA 2000 ms / 30 ms / 90°, FOV 220 × 220 × 120 mm^3, acquisition matrix 80 × 80, slices 30, slice thickness 4 mm and number of repetitions 234. Three presentations of each odorant concentration (6s per stimulation) were presented to the subject's nostrils sequentially with a 30s period of odorless air between each stimulation. A home-built olfactometer was used with a flow rate of 8 L / min to synchronize with image acquisition and visual cues.

Data Processing and Analysis The fMRI data were normalized to the Montreal Neurological Institute brain template [2] and group analyses (student *t-tests*, ANOVA) on volume and location of olfactory activations were performed using SPM5 [3].

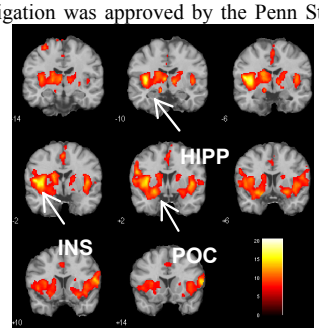

Figure 1: Average olfactory activation at all 4 lavender concentrations in healthy subjects (n=10, one-sample *t-test*, family-wise correction, p<0.05).

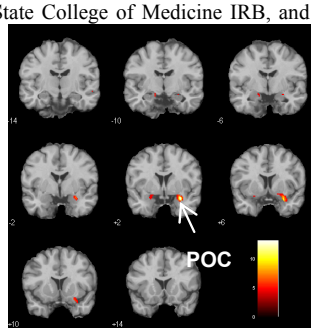

Figure 2: Olfactory activation difference between two sequential runs of the same stimulation paradigm in healthy subjects (n=10, paired *t-test*, uncorrected, p<0.001).

Results: As shown in Fig. 1, significant bilateral activations were obtained in primary olfactory cortex region (POC), hippocampus, insular cortex, and thalamus in both runs of an olfactory fMRI paradigm. However, as shown in Fig. 2, the second run of the identical paradigm yielded significantly less activation in POC, indicating a habituation effect sustained between the two runs. Fig. 3 and Fig. 4 show activated cluster size in POC and insular cortex respectively at each stimulus. Contrary to expectations, activation volumes in both structures exhibited a decreasing trend with sequentially increasing odorant concentration, demonstrating a habituation effect during the execution of the paradigm.

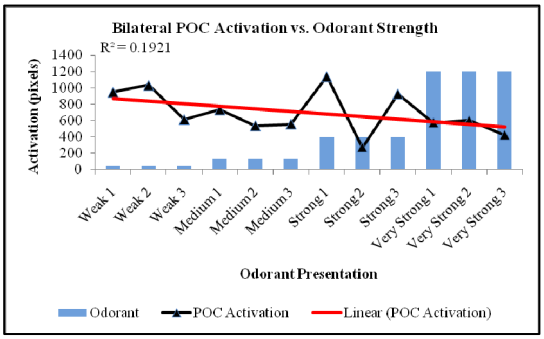

Figure 3: Activated cluster size of POC at each odorant concentration in healthy subjects (n=10, ROI analysis, one-sample *t-test*, uncorrected, p<0.001).

Discussion: One would expect the BOLD effect in POC to increase with increasing odorant concentration. The dynamic BOLD responses shown in Fig. 3 and Fig. 4 are likely modulated by a habituation mechanism triggered by increasing odorant intensity, which makes BOLD response no longer a linear system. As shown in Fig. 2, the activation decrease in the second runs suggests that habituation may last more than 5 minutes in POC. In this case, the BOLD response to a set of stimuli was influenced by the previous odorant exposures, which is a typical nonlinear characteristic. Although such behavior in olfactory fMRI data has been observed [4-7], the importance of habituation and the revealed nonlinear characteristics in the BOLD signal have not been adequately addressed.

First, the habituation effect shown here invalidates the fundamental assumption of linearity of BOLD response in the brain. The BOLD signal in the olfactory system may be modulated and varied throughout the paradigm. Thus, current dogma for fMRI data analysis may require modification.

Secondly, the sustained habituation effect shown in Fig. 2 must be considered in the test-and-retest studies required for clinical research. Lastly, the dynamic patterns of olfactory BOLD response in Fig. 3 and Fig. 4 are paradigm-dependent. The observed temporal change in BOLD signal is the combined result of odorant concentration, air flow rate, respiration pattern, and the duration and sequence of odorant delivery.

In summary, olfactory BOLD response demonstrates a dynamic characteristic due to habituation triggered by our olfactory fMRI paradigm and suggests that a nonlinear model should be considered. Such a nonlinear model is important beyond the analysis of olfactory fMRI and may also apply to pain and other neuronal network systems with a feedback mechanism.

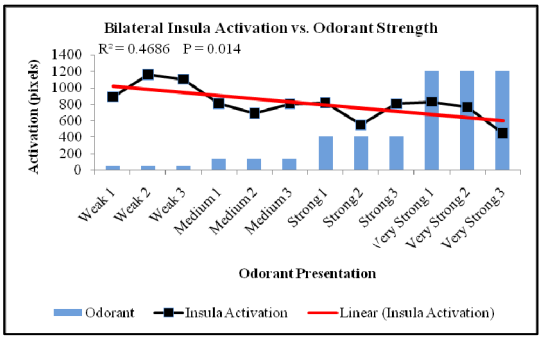

Figure 4: Activated cluster size of insular cortex at each odorant concentration in healthy subjects (n=10, ROI analysis, one-sample *t-test*, uncorrected, p<0.001).

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