Event-related Olfactory fMRI

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Introduction

There is an increasing interest in conducting olfactory fMRI since central olfactory system is known to be involved in a number of prevalent neurologic diseases such as AD, PD and PTSD [1-3]. However, olfactory system has received a limited number of fMRI studies partly due to the technical difficulties in reliable odor stimulant delivery. Because of the relatively low frequency and high individual variability of the respiration, traditional block design paradigms produced poor fMRI results. Thus, in recent studies, the subjects were trained to follow either visual or audio instructions for breathing or sniffing to synchronize the odor stimulation [4,5]. Such methods not only involve multiple central nervous systems in addition to olfaction, but also complicate data analysis; and they may fail in studying neurological and psychiatric diseases as some patients will not be able to follow the breathing instructions. Here we present an event-related paradigm design and post-processing tools for olfactory fMRI without requirement to control the subject's respiration or sniffing.

Methods

Odor Stimulation paradigm The olfactory stimulation paradigm was executed by an olfactometer (Emerging Tech Trans, LLC, Hummelstown, PA, USA), which can deliver up to 6 different odorants to the subject's nostrils accurately without any optical, acoustic, thermal, or tactile cues to the subject. The olfactometer was triggered by the TTL pulses from the MR scanner and the TTL pulses were recorded to synchronize the odorant stimulation paradigm with respiration and MRI timing protocol. Lavender oil diluted in 1,2-propanediol (Sigma) at 0.10% (v/v) was used as the olfactory stimulant. The base stimulation paradigm was 6 sec odorant stimulation repeated twelve times and interleaved with 30 sec odorless air at a constant air flow of 6 L/min. The base paradigm was executed twice in two separate runs with no consideration of respiration. Subsequently, the base paradigm was repeated twice with odor onset triggered by the *effective inhalations*. There were no cues for smell or instruction for respiration provided to the subject, and the subject was not asked to provide any response during the scan protocol.

fMRI Study Protocol fMRI images of the entire brain were acquired four times from a healthy 24 year-old male subject with normal olfaction function on a Siemens 3 T system with a 8-channel coil for reception. T_2*-weighted EPI sequence was used with an acceleration factor of 2, TR / TE / FA = 2000 ms / 30 ms / 90°, FOV = 220 × 220 mm^2, acquisition matrix = 80 × 80, 30 axial slices with a slice thickness = 4 mm, number of repetitions = 212 for base paradigms and 245 for inhalation triggered paradigms.

Data Processing and Analysis The respiration data and odor stimulation timing and image acquisition timing data were processed with qMRI [6]. Each respiratory cycle during odorant delivery was segmented into slow inhalation, fast inhalation and exhalation periods. Instead of locating the onset vectors and durations for the block-design paradigm, each of the above three periods was considered an event in an event-related paradigm. The fMRI data were normalized to the MNI brain template [7] and olfactory activation maps were processed with the event-related stimulation paradigm using SPM5 [8].

Results & Discussion

Figure 1 shows some representative respiration time-courses and effective fMRI paradigms (left) and corresponding activation maps responding to the odor stimulations (right). The effective inhalations (slow phase and fast phase) were obtained by convolving respiration curve with base-paradigm. When the odor delivery was triggered by effective inhalations, during the fast inhalation phase (event), significant olfactory activation was observed in the orbitofrontal cortex, inferior, anterior and superior insular cortex, and cingulate cortex (Fig. 2 bottom right). In contrast, during the slow inhalation phase (event), odorant only elicited limited activation, mainly in the left anterior insular cortex. No significant brain activation responding to the odorant was observed during the exhalation phase (event) at the same statistical level. When the odor delivery was not triggered by respiration, only limited olfactory activation was observed at the right anterior insular cortex during the fast inhalation phase, and no significant activation was observed during the other two phases.

Our data showed that the subject's respiratory modulation of the olfactory stimulation paradigm significantly confounded the BOLD signal. Thus, it is critical to incorporate respiration into both paradigm design and data processing in order to produce reliable olfactory fMRI data. This is particularly important for studies of brain responses to odorant stimulation but not sniffing [9]. The presented olfactory fMRI event-related design and corresponding data processing method are simple and effective for generating olfactory fMRI results with minimal confounding variability. This experimental set-up is also ideal for studies of olfactory deficits in early AD and PD subjects as it requires minimal participation from the subject during data acquisition.

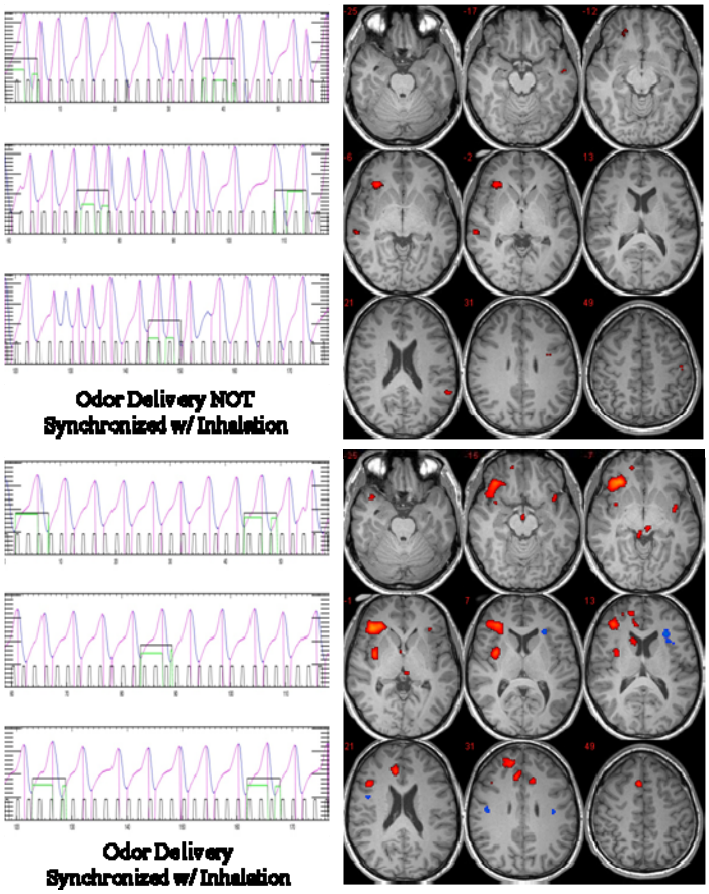

Fig. 1: Representative respiration time courses (left) and corresponding activation maps (right) during odor stimulation paradigm: top, base odor stimulation paradigm; bottom, odor delivery triggered by effective inhalation. Pink: inhalation; blue: exhalation; black boxes: odorant presentations; green: effective inhalation, where height represents the depth of respiration movement; small bars: image acquisition markers. Brain olfactory activations during fast inhalations (red) and slow inhalations (blue) (uncorrected, $p < 0.001$, extent threshold = 6). There was no significant olfactory activation during exhalation period.

References

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