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RESEARCH NOTE

A mismatch process in brief delayed matching-to-sample task: an fMRI study

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Abstract Our previous ERP studies have consistently demonstrated that a negativity N270 elicited by incongruent information in visual S1–S2 matching task represents a type of conflict process, which is distinct from that represented by the classic conflict task or other negative components in delayed matching-to-sample stimulus presentation patterns, since the inter-stimulus interval between S1 and S2 was presented as shorter as 500 ms. The N270 component of ERP was shown to reflect conflict processing during the simple working memory operations. In the present study, a functional MRI (fMRI) was used to investigate the visuospatial characteristics of brain activation associated with the task eliciting N270. The fMRI data showed an increased activation in the right anterior cingulate cortex (ACC, BA 24) and right dorsolateral prefrontal cortex (DLPFC, BA 46), and activation biased to the left occipito-temporal cortex (BA 37) in the incongruent condition. It is suggested that the greater activations of the right ACC coupling with right DLPFC to incongruent task reflect functional efficiency of the right cingulo-prefrontal network during the brief visual delayed period discrimination performance and mismatched information processing.

Keywords Delayed matching-to-sample task · Functional magnetic resonance imaging (fMRI) · Mismatch · Anterior cingulate cortex · Dorsolateral prefrontal cortex

This work was approved by the local ethics committee.

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Introduction

Our previous studies using event-related potentials (ERPs) have consistently revealed negativity (N270) in a visual S1–S2 matching task. This N270 occurs only when an attribute (e.g. shape, color, position, face and arithmetic calculation) of the second stimulus (S2) showed some discrepancy from the first one (S1). Another important parameter to N270 elicitation is that the inter-stimulus interval (ISI) should be ranged from 300 to 1,000 ms (Cui et al. 2000; Kong et al. 2000; Zhang et al. 2002, 2005; Wang et al. 2003). Topographically, the N270 is distributed mainly on the fronto-central as well as slightly on bilateral temporo-posterior scalp (Zhang et al. 2003, 2005). In these studies, results indicate that either the information discrepancy in stimulus itself or mentally generated mismatched information can produce a N270. It implicates that the N270 could be an indication of endogenous activity that

serves as a timing index for the mismatch processing in the brief delayed matching-to-sample (DMS) task (Kong et al. 2000; Zhang et al. 2001, 2002, 2005).

Brain regions associated with match and mismatch processes using DMS task have been frequently assessed by multiple studies. Prefrontal cortex seems to play a necessary role in delayed response in non-human primates studies and human neuroimaging studies. In monkeys, electrophysiological data have showed that some frontal neurons are selective responses to the testing stimuli depending on whether or not they matched the sample stimuli (Miller et al. 1996; Takeda and Funahashi 2002). Human neuroimaging data have identified a number of frontal as well as posterior brain areas involved in some kinds of delayed-recognition performances (Haxby et al. 2000). A recent study indicated greater activity in dorsolateral prefrontal cortex (DLPFC) for stimuli that matched the sample stimuli than those that did not in a face recognition task (Druzgal and D'Esposito 2001). However, the findings of these studies appear to be variable in the specific type of cognitive components due to differences in experimental design. For example, Leung et al. (2005) have examined the difference between negative probe (mismatch) and positive probe (match) in delayed recognition task. They confirmed that the right prefrontal cortex showed greater activation to the negative probe than to the positive probe, and the opposite effect was not observed. The differential prefrontal activations to DMS tasks were interpreted as attributions to delayed item recognition tasks, which indicate that prefrontal cortex plays an important role in strategic memory organization.

In this study, we used event-related fMRI to investigate brain activations associated with delayed response task at fast inter-stimulus interval (500 ms) which evoked negativity N270 in response to incongruent task in ERPs. The inter-stimulus interval here was shorter than traditional DMS paradigms that the ISI was lengthened more than 1,000 ms. We hypothesized that, in addition to activations overlapped with other delayed recognition tasks, there would be task-specific neural substrate responses. Results were expected to identify the brain regions engaged in conflict processing during the brief DMS task.

Materials and methods

Subjects. Twelve healthy, right-handed undergraduates (6 men and 6 women; age from 22 to 25), participated in this study. All subjects had normal or corrected to normal vision. Each subject performed the same task during MR scanning. This work was approved by the local ethics committee of PLA General Hospital. Informed consents were obtained from all subjects prior to the beginning of the experiments.

Task. The task used in the present study is similar to that used in ERP studies (Cui et al. 2000). Prior the fMRI study, we had tested the longer inter-trial interval (ITI) that would be used in MRI camera room. The ITI was the only difference of fMRI design from ERP stimulus pattern. It was found that the typical negative component N270 elicited was the same as the findings in our previous ERP work. Therefore, the activation of the ERP and fMRI should produce no significant difference.

A test and a control condition were used. In the test condition, visual stimuli consisted of simple geometric shapes, like square, rectangle, triangle and star displayed in white against a black background. There were two types of stimuli: congruity (same shape) and conflict (different shape). The stimulus exposure of S1 and S2 was 300 ms each, and the inter-stimulus interval (ISI) was 500 ms. The inter-trial interval (ITI) was randomly varied between 4 s and 18 s, allowing hemodyamic responses to peak. The average ITI was approximately 12 s. The subjects were instructed to indicate whether S1 and S2 were the same as quickly and accurately as possible with a key box in each of the left and right index fingers. A total of 36 trials, 12 for incongruence, 12 for congruence and 12 for control, were presented randomly with equal probability. For the control condition, the subjects were instructed to respond to the onset of a cross only. Test and control trials were presented alternately. The presentation order and the hand used by the subject to respond were counterbalanced within subjects. The functional scanning session lasted 10 min and 40 s.

fMRI acquisition and data analysis

fMRI data acquisition

fMRI data were acquired on a 1.5 Tesla GE Signa system with echo planar imaging (EPI) at the Department of Radiology, The Chinese People's Liberation Army General Hospital in Beijing. The subjects wearing earplugs were positioned supine in the scanner. Their head movement was snugly constrained with foam pads and a belt. The stimuli were presented in white on a dark screen viewed from within the MR scanner through a mirror above subjects. The stimulus size was about 2°.

Scanning began with a number of localizer scans used to orient the functional scans approximately parallel to the anterior–posterior commissure (AC-PC) line. Twelve axial slices were acquired with a T2*-weighted gradient echo single-shot echoplanar imaging (EPI) pulse sequence (thickness/gap = 6/1 mm, matrix size = 64 × 64, TR = 2,000 ms, TE = 40 ms, flip angle = 90°, FOV = 240 × 240 mm). A total of 320 EPI volumes were obtained from each subject. The acquisition of each EPI volume was synchronized with the onset of a visual stimulus. At the same

position, 60 slices by spin echo sequence (thickness = 2.5 mm, no gap, TE = 2.1 ms, matrix size = 256 × 256, flip angle = 30°, FOV = 240 × 240 mm) were then acquired. Finally, a high-resolution anatomical 3D T1-weighted images (TR = 500 ms, TE = 14 ms, thickness/gap = 6/1 mm, in-plane resolution = 256 × 192, FOV = 240 × 240 mm) of the whole brain were acquired.

fMRI data analysis

fMRI data processing and analysis were conducted on a SUN SPARC workstation running the Red Hat Linux 6.2 operating system. The first four volumes of each subject were discarded, and the remaining 316 EPI volumes were used for further analysis. All the functional images were then registered to the volume collected nearest in time to the high-resolution SPGR anatomical scan to correct potential small head motions using the motion correction module of the AFNI 2.2 software package (Cox 1996). Two boxcar reference functions for incongruent and congruent stimuli were built according to the time series of their presentation, convolved with γ-variate function to account for the slow hemodynamic response. A linear regression was then used to calculate the least squares fit of each voxel time series to the reference function by which the response to each condition at each voxel was indicated. This generated activation maps for each condition of each subject.

Individual activation maps were co-registered to the 3D structure images and normalized according to the standard coordinates defined by Talairach and Tournoux atlas (1988). The images were re-sampled at 2 mm × 2 mm × 2 mm and smoothed with an isotropic Gaussian kernel (FWHM = 6 mm). Group composite maps were generated after transforming the individual maps into a standardized coordinate system. A bootstrapping randomization technique (applied in Leung et al. 2002) was used to calculate the contrast maps such as incongruence versus congruence conditions. The composite maps were cluster-filtered and thresholded ($P < 0.005$) to reveal only pixel clusters with percent signal change values that fall above the 99.5 percentile of the random sampling distribution.

Activation region-of-interests (ROIs) were defined based on the activations obtained from the subtraction of brain activity between incongruent and congruent conditions. The ROIs included the bilateral anterior cingulate cortex (ACC), DLPFC, inferior parietal lobule and occipitotemporal cortex (OTC). The average percent signal change from baseline was calculated for each ROI of each condition. Percentage change of signal was calculated using $(A - B)/B \times 100$, where A and B were the averaged signals of the conditions (incongruence or congruence) and the baseline of the task respectively. The time course of each condition was determined for each ROI. For each individual, the average percentage changes in signal at each time point were calculated relative to the mean signal during baseline. Time differences in slice acquisition were adjusted for each slice. Before performing the interpolation and resampling, all time course data were time-smoothed by a Gaussian filter. In order to quantify the significance of the differences between the hemodynamic responses for the two conditions, the peak (average of the values for time points 5 and 6) of this response was computed for each condition for each subject. A paired t test (one tail) was then performed over all subjects to determine if the incongruent condition was significantly different from the congruent condition. The significance values reported in the present study are from this comparison.

Results

Behavioral data. Behavioral results showed significantly longer reaction times to both conflict and congruity trials (624 and 517 ms respectively) than to the control (435 ms). The reaction times in incongruent trials were significantly longer than in congruent trials ($t_{(11)} = 3.47$, $P < 0.01$), while the difference between incongruent and congruent trials in accuracy rate was not significant (average 98%, $P > 0.05$).

Activations during the DMS task

In this brief DMS task, common brain areas activated by both incongruent and congruent stimuli were in the ACC (BA 24/32), DLPFC (BA 9/46), inferior parietal lobule (BA40) and OTC (BA 37/39), in comparison with the control. Most of the activations were bilateral, except the precuneus activation which predominantly appeared to be right lateralized.

Incongruent versus congruent trials

We focused on examining the difference between the two stimuli conditions (incongruence and congruence) of the task. All the selected ROIs were activated above the fixation baseline for both conditions. Direct contrast between the two conditions revealed that the right ACC (Fig. 1a), right DLPFC (Fig. 1b) and the left OTC (Fig. 1c) were more activated in response to the incongruent than to the congruent condition ($P < 0.005$, uncorrected). No brain areas show greater activation to the congruent condition than to the incongruent condition even when the threshold was lowered to $P < 0.05$ (uncorrected). Average percentage changes in signal over time for selected ROIs during the incongruent and congruent trials of the task are shown in Fig. 2. The response in the incongruent condition is almost equivalent to that in the congruent condition in the regions of left ACC ($t_{(11)} = 2.75$, $P = 0.13$), left DLPFC

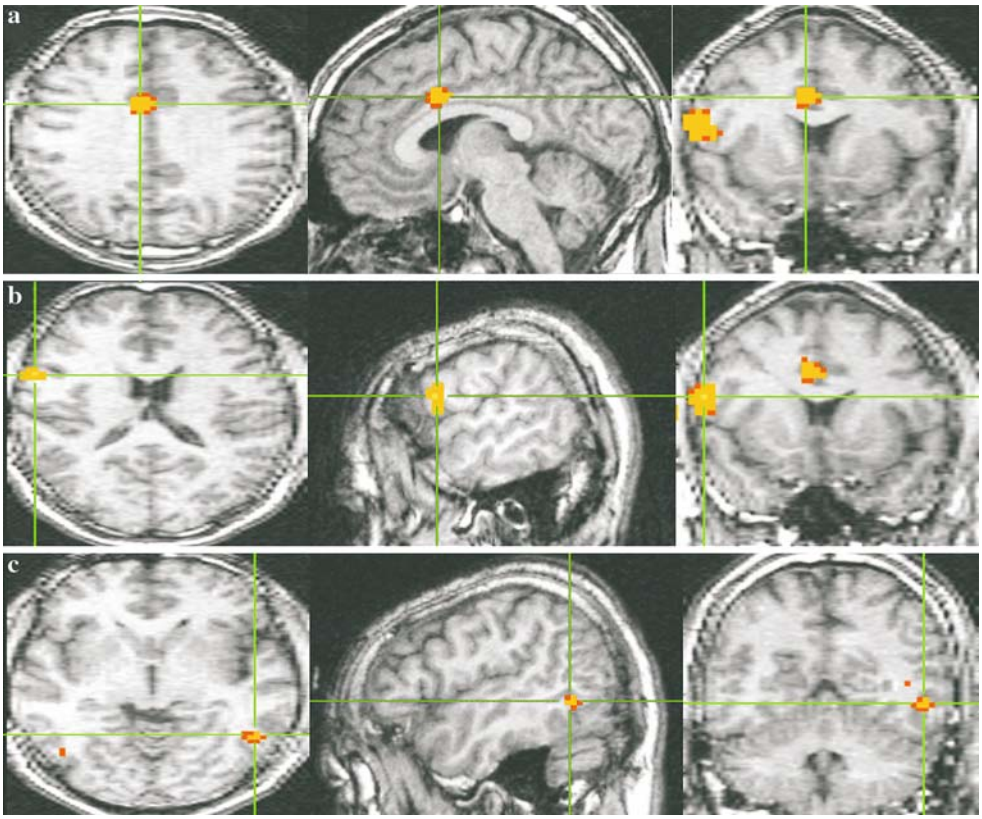

Fig. 1 Average of Talairach normalized brains ($n = 12$) showing the activation pattern produced the comparison (incongruent minus congruent): **a** the right ACC (BA 24), **b** the right DLPFC (BA 46), and **c** left OTC (BA 37). No brain areas show greater activation to the congruent condition than to the incongruent condition. The left side of the brain is shown to the right

($t_{(11)} = 3.16$, $P = 0.10$) and right OTC ($t_{(11)} = 2.87$, $P = 0.14$), while the response in the incongruent condition in the right ACC, right DLPFC and left OTC is significantly enhanced in comparison to the congruent condition during the brief DMS task (see below).

To further determine whether the activation to the incongruent showed by the group level analysis was different from the congruent in these brain regions, separate ROI analysis was conducted. Activations in the selected ROIs were compared across the two stimuli conditions. A region [bilateral ACC (BA 24), DLPFC (BA 46), inferior parietal lobe (BA 40) and OTC (BA 37)] by condition (incongruence and congruence) interaction indicated that these regions were differentially engaged across the stimuli types ($F_{(7,77)} = 6.00$, $P < 0.001$). We performed paired t tests to confirm that the activations of the right ACC ($t_{(11)} = 8.47$, $P < 0.01$), right DLPFC ($t_{(11)} = 14.71$, $P < 0.003$) and the left OTC ($t_{(11)} = 6.05$, $P < 0.03$) to the incongruent and the congruent condition were significantly different, respectively. The activation of the right OTC ($t_{(11)} = 3.37$, $P = 0.07$) was shown to be marginally significantly greater in the case of the incongruent condition than that of the congruent condition. No significant difference was observed at inferior parietal lobule.

Incongruent effect in ACC and DLPFC

In order to examine the incongruent effect in the ACC (BA 24) and DLPFC (BA 46), repeated ANOVA with the incongruence/congruence condition and the right/left laterality as two key parameters was performed to analyze the average percent signal change from baseline across the subjects. The incongruence was more activated in general, indicated by main effect of condition ($F_{(1,11)} = 15.73$, $P < 0.001$) and of laterality ($F_{(1,11)} = 27.39$, $P < 0.001$). The tests indicated that the incongruence was significantly greater in the right ACC ($F_{(1,11)} = 37.30$, $P < 0.001$) and right DLPFC ($F_{(1,11)} = 41.00$, $P < 0.001$) than the corresponding left area.

Discussion

The paper reported the brain activations to fast inter-stimulus interval of delayed response task using event-related fMRI, a method rarely employed in neuroimaging study. As expected, we observed widespread brain activations during the incongruent trial that mostly overlapped with activations during the congruent trial. Our focus was on examining the role of DLPFC and ACC during brief

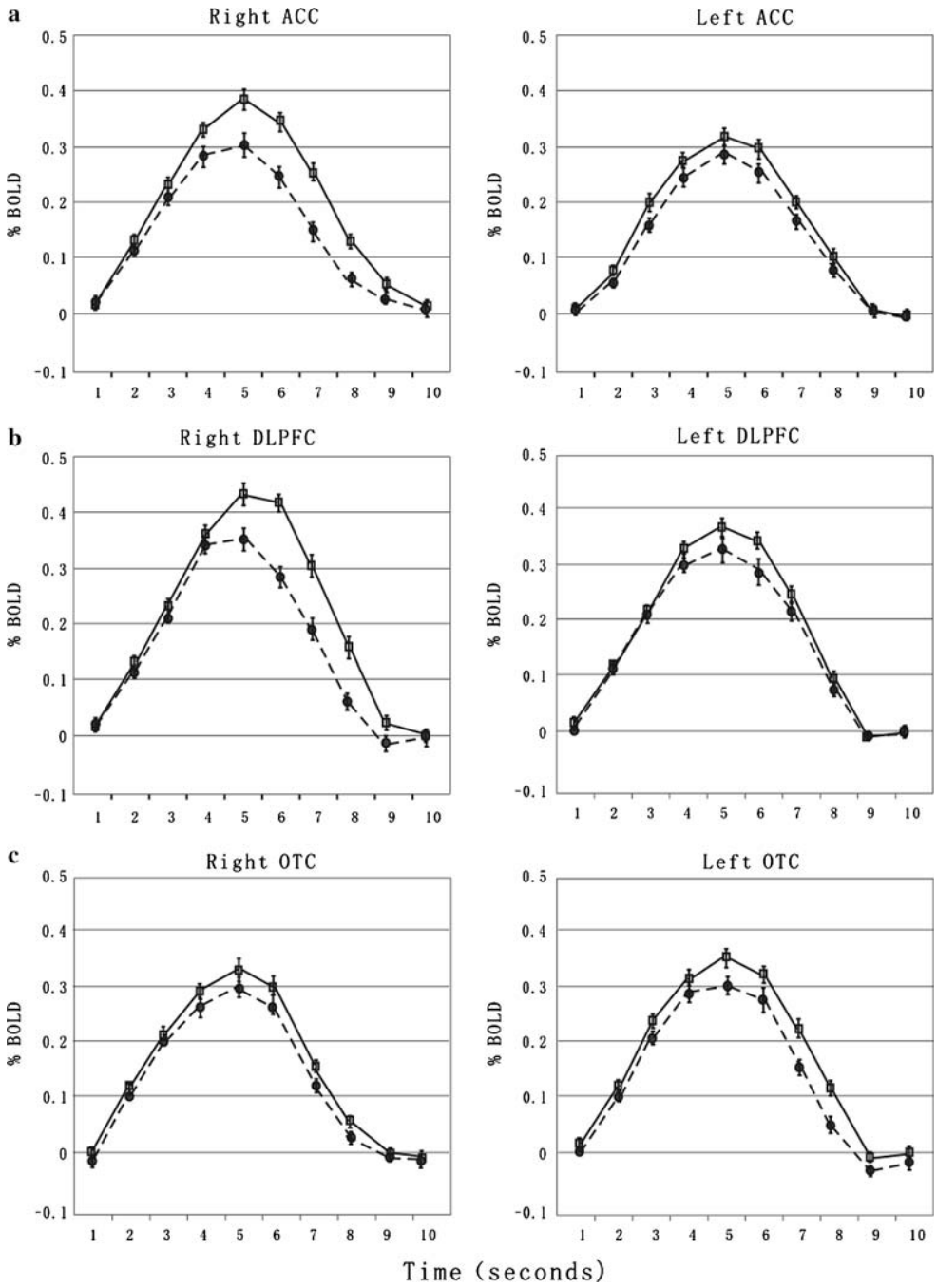

Fig. 2 Event-related BOLD response (% change over fixation baseline) averaged over all subjects in the bilateral ROIs of **a** ACC (BA 24), **b** DLPFC (BA 46) and **c** OTC (BA 37) selected from activation maps. The averaged BLOD response to incongruent condition (*solid line*) shows significantly greater than to congruent condition (*dashed line*) in the right ACC, right DLPFC and left OTC. The response in the incongruent condition is almost equivalent to that in the congruent condition in the regions of left ACC, left DLPFC and right OTC. Statistical significance of these differences is given in the text. (*Error bars* reflect the standard error of the BOLD difference scores)

delayed period of visuospatial task since these regions have been particularly emphasized in DMS response of working memory. It is found that the right DLPFC, right ACC and left OTC were more active in response to incongruent than to congruent trials. The findings thus are consistent with previous evidence in supporting the proposal that the DLPFC and ACC are involved in recognition of working memory (Kerns et al. 2004; Kondo et al. 2004; Lei et al. 2006).

Previous neuroimaging studies have demonstrated that the ACC activation is mainly associated with signaling the presence of processing conflict, while the DLPFC is involved in the implementation of control in situation of conflict, indicating a dissociation in function of these regions (Macdonald et al. 2000; Botivinick et al. 2001; Kerns et al. 2004). Although such dissociation may not be possible in the present study, it can be reasoned that the DLPFC is consistently activated during the brief DMS task in terms of executive function, whereas ACC is only active in the context of mismatching stimulus type. That is, in matching situation, the activation of the ACC should be increased on mismatch trial, whereas the activation of the

DLPFC should not differ between the stimulus types. However, present findings show that greater activity is observed not only in the ACC but also in the DLPFC on the incongruent trials, suggesting that the two regions are concurrently involved in mismatched information during the brief delayed period of visuospatial performance.

The greater DLPFC activity to incongruent trials than congruent trials has been observed by previous report that found greater activity in this region for stimuli that mismatched the sample stimuli than those matched in spatial delayed response task (Leung et al. 2005). Perhaps one of the main functions of DLPFC is to compare with the current information mismatched or conflicted with the information maintained in working memory (Leung et al. 2005). If that is the case, the finding would suggest that greater DLPFC activity may provide the evidence that this area is also involved in qualitative differences in processing that distinguish shape incongruent and congruent stimuli in the present study. Another possibility is that the comparison process may require larger attention demand for the mismatched information, since our participants showed longer reaction times for the incongruent trials than the congruent trials.

Additionally, the present study detected significant ACC and DLPFC activations between stimulus types only in the right hemisphere. These regions are activated more in incongruent trails than in congruent trials. It may indicate the characteristics of hemispheric asymmetry of executive processes in the prefrontal regions. Previous neuroimaging studies have indicated that the functional cooperation between the ACC and DLPFC is neural bases for executive processes (D'Esposito et al. 1995; Bunge et al. 2000; Smith et al. 2001), and the function of the left and right singulo-prefrontal networks varies with the modality of tasks (Stephan et al. 2003; Kondo et al. 2004). Human case studies suggest that the left frontal damage is associated with memory deficits involving semantic items and right frontal damage with visuospatial items (Fuster 1997). Stephan et al. (2003) used letter- and visuospatial-decision tasks to confirm that verbal and visuospatial cognitive processes are functionally lateralized in the left and right hemispheres, respectively. Kondo et al. (2004) also reported that the right cingulo-prefrontal network is dominant in visuospatial task performance. These results indicate that the visuospatial cognitive processes are modulated by top-down control of the ACC and DLPFC, particularly in the right hemisphere (Kondo et al. 2004). In the present study, the enhanced activity in the right ACC coupling with right DLPFC in comparisons of incongruent versus congruent task may reflect functional efficiency of the cingulo-prefrontal network during the brief visual delayed period performance and mismatched information processing.

Taken together, the activation of the right ACC accompanied by the activation of the right DLPFC might play a major role in contributing to incongruent trial at fast ISI which evoked negativity N270 in ERPs. This hypothesis has also been confirmed by our recent study in patients with mild cognition impairment (MCI). We observed deficits in the amplitude of mismatch activity related to the correction of response in these MCI patients, associated with mismatch-resolution of the right DLPFC in this illness (unpublished).

In the present study, the bilateral OTC (BA 37) activations also showed marginal significant difference between incongruent and congruent tasks. This is consistent with other studies on the processing of shape information in the visual experiments (e.g. Curtis and D'Esposito 2003), reflecting the mismatch executive operations exerted on memory representation in the posterior regions.

Conclusion

In the present study, event-related fMRI was used to investigate brain activations associated with delayed response task at fast inter-stimulus interval. As expected, results indicate differential information processing between incongruent and congruent tasks. The right ACC (BA 24) and right DLPFC (BA 46) were more activated to the incongruent task. The greater activations of the right ACC coupling with right DLPFC to incongruent task may reflect functional efficiency of the right cingulo-prefrontal network during the brief visual delayed period discrimination performance and mismatch information processing.

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