

## A

■ It is well documented that the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) are intensively involved in conflict control. However, it remains unclear how these “executive” brain regions will act when the conflict control process interacts with spatial attentional orienting. In the classical spatial cueing paradigm [Posner, M. I., & Cohen, Y. (1984). Components of visual orienting. In H. Bouma & D. G. Bouwhuis (Eds.), *Attention and performance X* (pp. 531–556). Hillsdale, NJ: Erlbaum], response to a target is delayed when it appears at the cued location compared with at the uncued location, if the time interval between the cue and the target is greater than 300 msec. This effect of inhibition of return (IOR) can alter the resolution of Stroop conflict such that the Stroop interference effect disappears at the cued (inhibited) location [Vivas, A. B., & Fuentes, L. J. Stroop interference is affected in inhibition of return. *Psychonomic Bulletin and Review*, 8, 315–323, 2001]. In this event-related functional magnetic resonance study, we investigate the differential neural mechanisms underlying interactions between pre-

response interference, response interference, and spatial orienting. Two types of Stroop words [incongruent response-eligible words (IE), incongruent response-ineligible words (II)] and neutral words were presented either at the cued or uncued location. The significant pre-response interference at the uncued location activated the left rostral ACC as compared with at the cued location. Moreover, although the IE words which have conflicts at both pre-response and response levels did not cause significant behavioral interference at the cued location, they activated the left DLPFC as compared with at the uncued location. Furthermore, neutral words showed significant IOR effects behaviorally, and they activated the left frontal eye field (FEF) at the uncued location relative to the cued location. These results suggest that the left rostral ACC is involved in the interaction between pre-response conflict and IOR, whereas the left DLPFC is involved in the interaction between response conflict and IOR. Moreover, the FEF is involved in shifting attentional focus to novel locations during spatial search. ■

Both the anterior cingulate cortex (ACC) and the dorsal lateral prefrontal cortex (DLPFC) have been well documented as playing an important role in cognitive control such as monitoring and resolving conflicts (Kerns et al., 2004; see Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004 for a recent review). However, it is not yet clear whether these brain regions will be differentially recruited when the conflict resolution process is modulated by attentional orienting, that is, when the stimuli that lead to conflicting cognitive processes are in or out of attentional focus. The aim of the present event-related functional magnetic resonance imaging (fMRI) study was to investigate the neural correlates for the interaction between spatial attention and conflict processing. In particular, we examined whether the pattern of this interaction depends on the nature or level of the conflict.

The classical Stroop task provides an important tool for researchers to investigate the neural correlates of conflict control. Using fMRI or other brain imaging techniques, a large number of studies found that when subjects are asked to name the color of a Stroop word, interferences from the activation of the irrelevant word meaning induce activities in several brain regions, including the ACC and the DLPFC (e.g., Milham, Banich, Claus, & Cohen, 2003; Zysset, Muller, Lohmann, & von Cramon, 2001; Banich et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000). These activities may indicate different roles that different brain regions play in the conflict control processes. On the other hand, the Stroop interference may take place at different levels of information processing, from stimulus encoding to response execution. The locus of the interference effect can be differentiated experimentally into pre-response and response levels (e.g., Milham et al., 2001; Eriksen & Schultz, 1979).

Suppose subjects are asked to judge whether the color of a word is red or green by pressing corresponding

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response keys. The task-irrelevant word meaning of

monitoring system because of the lack of attentional resources. Thus, the ACC should not be activated when stimuli were presented at the cued location, irrespective of the type of Stroop words. Given the assumption that the ACC is responsible for the evaluation of conflicting information and the DLPFC is responsible, together with posterior brain regions, for the resolution of conflict (Botvinick et al., 2001, 2004; MacDonald et al., 2000), one might predict that the DLPFC will not be activated in this situation either. In contrast, the IT hypothesis assumes that the absence of interference effect at the cued location was because the connection between the pre-response representation and its corresponding response code is temporarily blocked for stimuli at the cued location, which implied that the IT mechanism is likely to apply at the response level rather than at the pre-response level. Fuentes et al. (2000) applied the combined manipulation of IOR and Stroop interference to schizophrenic patients, who have been shown to have dysfunction of the DLPFC (Shenton, Dickey, Frumin, & Robert, 2001; Pol, Baaré, Gispén-de Wied, Mali, & Kahn, 1995). They found that these patients, unlike normal participants, did not show any reduction of the Stroop effect at the cued location. Therefore, the IT hypothesis predicts strong prefrontal activation at the cued location for the Stroop interference, especially for the conflict at the response level. Moreover, given the present experimental design, we will also examine the neural basis of IOR, which has been localized in the parietal cortex and frontal oculomotor regions (e.g., Mayer, Seidenberg, Dorflinger, & Rao, 2004; Lepsien & Pollmann, 2002). We expect that the IOR effect is associated with neural activities in the parietal–frontal network.

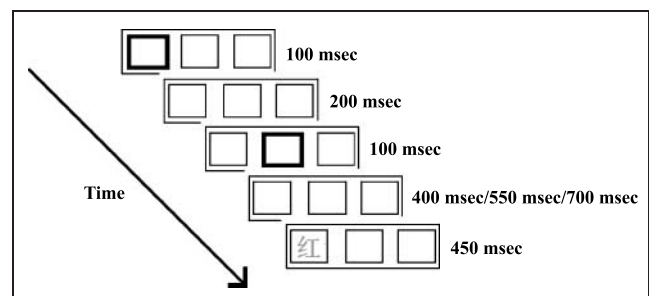
Twelve undergraduate and graduate students (7 women, range 21–29 years) participated in the present study. All of them were right-handed and had normal or corrected-to-normal vision without color blindness or weakness. All the subjects gave written informed consent before scanning and none of them had a history of neurological or psychiatric disorders. This study was approved by the Academic Committee of Department of Psychology, Peking University.

The experiment had a 2 (cue validity: cued vs. uncued)  $\times$  3 (stimulus type: incongruent response-eligible vs. incongruent response-ineligible vs. neutral) factorial design. Participants were asked to make discrimination response to the color of the target word (written in Chinese character), pressing one key if the color was red and another key if the color was green. The words used

for IE stimuli were “green” and “red” (“绿” and “红” in Chinese), whereas those for II stimuli were “yellow” and “blue” (“黄” and “蓝” in Chinese). For these two types of stimuli, the word meaning and the color of the word were always incongruent. The neutral words consisted of four single-character words unrelated to color but were matched with the incongruent words in terms of frequency and orthographic structure. Each experimental condition had 48 trials, with the combination of character and color balanced over trials.

The stimuli were presented through an LCD projector onto a rear projection screen located behind the participants’ head. Participants viewed the screen through an angled mirror on the head coil. All of the characters were  $1.3^\circ$  of visual angle. Each trial consisted of serial displays (Figure 1) of white boxes presented on a black background. Each box measured  $1.5^\circ \times 1.5^\circ$  and the center-to-center distance between two adjacent boxes was  $4^\circ$  in visual angle. For a trial, the outlines of one of the peripheral boxes became thicker and brighter for 100 msec to attract attention. Then three white boxes appeared for 200 msec, followed by a display in which the outlines of the central box became thicker for another 100 msec. The three white boxes were then displayed again for 400, 550, or 700 msec before the target was presented. The purpose of using variable SOAs between the cue and the target was to prevent participants from forming time-based expectations for the target. The target appeared in either the cued or the uncued peripheral box for 450 msec. The peripheral cue was uninformative with respect to the location of the target. Participants were asked to fixate at the central box all the time and to respond as quickly and as accurately as possible to the color of the target. Half of the participants used their left hand and half the right hand to make responses. The mapping between response keys and the index and middle fingers was counterbalanced over participants.

For the purpose of fMRI design, there were also 96 null trials, each of which consisted of displays with the same three white boxes, but with no flash cue or the target. The intertrial intervals were jittered from 3000 to 4000 msec (3000, 3250, 3500, 3750, and 4000 msec) with



1. Example of the sequence of events in a trial. The Chinese word used as the target was colored in actual presentation.

a mean interstimulus interval of 3500 msec. All participants completed a training section of 15 min before the scanning.

### 2.1.1. Procedure

A 3-T Siemens Trio system with a standard head coil at the Beijing MRI Center for Brain Research was used to obtain T2\*-weighted echo-planar images (EPI) with blood oxygenation level-dependent contrast (matrix size:  $64 \times 64$ , pixel size:  $3.4 \times 3.4 \times 5 \text{ mm}^3$ ). Twenty-four transversal slices of 4-mm thickness that covered the whole brain were acquired sequentially with a 1-mm gap (TR = 1.5 sec, TE = 30 msec, FOV = 220 mm, flip angle =  $90^\circ$ ). The first five volumes were discarded to allow for T1 equilibration effects. Images were spatially realigned to the first volume for head movement correction, interpolated in time (temporal realignment to the middle slice), and normalized to a standard EPI template volume (resampled to  $2 \times 2 \times 2 \text{ mm}^3$  voxels). The data were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate inter-subject anatomical variability.

### 2.1.2. Data analysis

Data were analyzed by using Statistical Parametric Mapping software SPM2 (Wellcome Department of Imaging Neuroscience, London; Friston et al., 1995), employing a random effects model. At the first level, six event types were defined, including cued incongruent response-eligible target (Cued\_IE), cued incongruent response-ineligible target (Cued\_II), cued neutral target (Cued\_N), uncued incongruent response-eligible target (Uncued\_IE), uncued incongruent response-ineligible target (Uncued\_II), and uncued neutral target (Uncued\_N). The event type was time-locked to the onset of the peripheral cue by a canonical synthetic hemodynamic response function and its first-order temporal derivative. Additionally, all the error trials were included as an extra regressor of no interest. The six head movement parameters were included as confounds. The obtained contrast images of the first-level analysis were entered into a second-level random effects group analysis. If there were no special illustrations, activations were reported at a height threshold of  $p < .001$ , uncorrected, and a cluster threshold of greater than 60 voxels.

### 2.1.3. Results

Mean reaction times (RTs) on correct trials and response error rates were calculated for each of the participants and experimental conditions (see Table 1) and then entered into  $2$  (cue validity)  $\times$   $3$  (stimulus type) analyses of variance (ANOVAs). Results showed that the main

**Table 1.** Mean Reaction Times (msec) and Percentages of Errors (%) as a Function of Cue Validity and Stimulus Type

|       | Cued |     |         | Uncued |     |         |
|-------|------|-----|---------|--------|-----|---------|
|       | IE   | II  | Neutral | IE     | II  | Neutral |
| RT    | 592  | 602 | 598     | 587    | 591 | 570     |
| SD    | 86   | 86  | 81      | 80     | 81  | 76      |
| Error | 2.8  | 3.3 | 2.1     | 2.4    | 1.7 | 3.1     |

IE = incongruent response-eligible; II = incongruent response-ineligible.

effect of cue validity was significant,  $F(1,11) = 6.76$ ,  $p < .05$ , indicating that RTs to targets at the cued location (597 msec) were slower than those at the uncued location (583 msec). This was the typical manifestation of the IOR effect. The interaction between cue validity and stimulus type was significant,  $F(2,22) = 4.91$ ,  $p < .05$ , indicating that the Stroop interference effects had different patterns at the cued and uncued locations. Further analysis examining the interaction between cue validity and pre-response conflict found a significant effect,  $F(1,11) = 5.91$ ,  $p < .05$ , suggesting that the pre-response conflict (“II–N”) at the uncued location [ $t(11) = 2.76$ ,  $p < .05$ ] was larger than that at the cued location [ $t(11) < 1$ ]. The combined pre-response and response conflict effect (“IE–N”) also significantly interacted with cue validity,  $F(1,11) = 7.633$ ,  $p < .05$ , suggesting that the combined pre-response and response conflict effect was significant at the uncued location,  $t(11) = 2.38$ ,  $p < .05$ , but not at the cued location,  $t(11) < 1$ . However, the response level conflict (“IE–II”) did not interact with cue validity,  $F(1,11) < 1$  (see Figure 2A).

On the other hand, the size of the IOR effect for IE, II, and neutral words increased linearly,  $F(1,11) = 7.63$ ,  $p < .05$  (see Figure 2B), but only the IOR effect for neutral words reached significance,  $t(11) = 5.59$ ,  $p < .001$ . This pattern of results replicated previous findings (Vivas & Fuentes, 2001). Analyses of error rates did not reveal any significant effects.

### 2.1.4. Discussion

Because there was a significant interaction between the pre-response conflict effect and the cue validity behaviorally, we first performed the F contrast “Uncued (II–N) versus Cued (II–N)” on fMRI data to explore the neural correlates underlying the interaction between pre-response conflict and spatial attention. Secondly, although there were no significant response conflict effects (“IE–II”) at either the cued or uncued location, differential neural activities may still underlie these two behavioral null effects (e.g., Fink, Marshall, Weiss, & Zilles, 2001). Specifically, if the nonsignificant Stroop interference at the cued location corresponded to a temporary disconnection between the irrelevant word

meaning and its response code, according to the IT account, we should expect to localize the neural correlates underlying this IT mechanism even without any apparent behavioral effects. Therefore, we performed an F test on the possible interaction between the response F

activation in the left frontal eye field (FEF, see Figure 3C). Further analysis on the extracted Beta values from the peak voxel in the left FEF showed that the left FEF was specifically activated by neutral words at the uncued location compared with those at the cued location,  $F(1,11) = 40.70, p < .001$ .

The main purpose of the current study was to investigate the neural correlates for the interaction between spatial attention and conflict processing. Behavioral data replicated and extended a previous study (Vivas & Fuentes, 2001) by showing that there were no Stroop interference effects at the cued (inhibited) location while both IE and II words produced significant interference

conflict and spatial attentional orienting. When attention is oriented to the new, uncued spatial location, the conflicting information there receives more attention resources and causes more interference, which accordingly evokes the general conflict monitoring mechanisms in the ACC. Moreover, this result demonstrates that the ACC is responsive to the pre-response level conflict, at least at the uncued location where attentional resources are abundant. This argument is consistent with the finding of Weissman et al. (2003), but inconsistent with the findings of Milham et al. (2001) and van Veen et al. (2001).

An issue in question is that most previous studies on conflict control found that the conflict control process is associated with activities in the dorsal or caudal region of the ACC (e.g., Badre & Wagner, 2004; Weissman et al., 2003; de Zubicaray et al., 2001; Milham et al., 2001; van Veen et al., 2001; see Botvinick et al., 2004, Ridderinkhof et al., 2004 for meta-analysis), whereas the present study observed activities in the rostral region. Reviewing a large number of studies, Bush, Luu, and Posner (2000) suggested that the ACC is a complex brain region with functionally distinct subregions. The dorsal region of the ACC is more frequently engaged by cognition whereas the rostral ACC and subcallosal portions of the ACC are more engaged in emotional behavior. However, this distinction is not absolute. Some cognitive tasks also activated the rostral ACC, whereas some other studies on emotion showed activation of the dorsal ACC (see Bush et al., 2000 for a review). It is possible that the neural activity within the ACC is critically dependent on the nature of task and response (van Veen & Carter, 2005; Milham et al., 2001, 2003; Bush et al., 2000).

Indeed, the rostral ACC has been reported to be activated in many tasks involving cognitive conflicts, such as in dual-task conditions (Dreher & Grafman, 2003) and in stimulus–response conflict tasks requiring speech utterance (Paus, 2001; Paus, Petrides, Evans, & Meyer, 1993) or manual response (Milham & Banich, 2005). Evidence from patient studies showed that the dorsal ACC is not necessary for cognitive control in both Stroop and go/no-go tasks (Fellows & Farah, 2005), whereas the more rostral part of the ACC plays important roles in modulating Stroop conflicts. Swick and Jovanovic (2002) found that damage to the left rostral to mid-dorsal ACC resulted in consistently lower accuracy on incongruent trials in the Stroop task, whereas damage to the right mid-caudal ACC was associated with normal levels of interference and accurate performance on incongruent trials. Thus, it seems that the rostral ACC, as well as the dorsal ACC, plays an important role in conflict control.

Other studies showed that the rostral ACC also plays a role in controlling spatial attention and spatial attention orienting (Small et al., 2003; Koski, Paus, & Petrides, 1998). Small et al. (2003) found that the rostral ACC (medial prefrontal cortex) was involved in voluntarily

allocating spatial attention when the distribution of attention must be regulated by internally generated expectations. Studies on patients with rostral ACC lesions also suggested that this region mediated the use of environmental cues to prepare for action (Alivisatos, 1992; Alivisatos & Milner, 1989) and that damage in this area may interfere with the ability to benefit from spatial cues in a target detection task (Koski et al., 1998).

Given the above evidence and given our experimental design in which both spatial attention and conflict control were involved, we would like to suggest that the rostral ACC is likely to be an important neural interface between spatial attention and pre-response conflict

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with predictions from the IT account (Fuentes et al., 1999, 2000).

Fuentes et al. (1999) combined the manipulation of IOR with the semantic priming task and found that the positive semantic priming effect at the uncued location became negative (i.e., longer RTs for the related targets than for the unrelated targets) when the prime and the target were presented at the cued location. This finding suggested that the semantic processing of the stimuli at the cued location was not compromised, but the access of the related target to its response code was inhibited. In the present study, responses to IE words at the cued location benefited from the disconnection between the activated task-irrelevant word meaning and its response code so that the Stroop interference effect was diminished at the cued location. Importantly, the present study suggested that the left DLPFC is responsible for preventing the task-irrelevant perceptual/semantic representation from contacting its response code.

A variety of evidence from monkey and human studies suggested that the DLPFC plays an important role in using the learned rule to select contextually appropriate response to a particular stimulus (Boettiger and D'Esposito, 2005; Schumacher, Elston, & D'Esposito, 2003; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Murray, Bussey, & Wise, 2000; Halsband & Freund, 1990; Petrides, 1982). For example, Koechlin, Ody, and Kouneiher (2003) suggested that the lateral prefrontal cortex played an important role in selecting premotor representations linking stimuli and responses and in exerting top-down control over the premotor cortex to bias the selection of a motor response. Schumacher et al. (2003) further showed that the left prefrontal cortex and the inferior parietal cortex were specifically involved in the nonspatial response selection. Such evidence implies that the parietal-premotor system represents possible stimulus-response (S-R) associations and the DLPFC interacts with this system to select the appropriate S-R mapping according to the task demand. Results from the present study suggested that the DLPFC may be responsible not only for selecting the correct S-R association for the task-relevant feature but also for



at the long SOA, we should observe differential brain activities. The left FEF activated by neutral words at the uncued location relative to the cued location suggests that this region is responsible for orienting spatial attention to the uncued novel spatial location.

To summarize, by combining the manipulation of spatial orienting with the Stroop task, the present study found that the rostral ACC is an important neural interface between pre-response conflict processing and spatial attention, whereas the left DLPFC underlies the neural interaction between response conflict and IOR. The left FEF is critically involved in orienting attention to the new uncued spatial location during IOR.

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