Distinct Neural Correlates for Resolving Stroop Conflict at Inhibited and Noninhibited Locations in Inhibition of Return

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Abstract

■ 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. *Psyc onomic 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. ■

INTRODUCTION

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 an incongruent word can correspond to a potential response (e.g., the word ''red'' or ''green'') or be outside the response set (e.g., the word ''blue''). The former type of incongruent words can be classified as response-eligible (IE) and the latter type as response-ineligible (II). Importantly, IE words introduce both competing phonological and semantic representations related to color and competing representations of the response output, whereas II words can only produce interference at the levels of semantics and phonology as the word meaning does not correspond to a potential response. Neutral words whose meanings are related to neither color nor potential responses can be used as a baseline to assess the degree of interference induced by IE or II words. Therefore, relative to neutral words, IE words can produce conflict at both the response and pre-response levels, whereas II words only generate conflict at the pre-response level. Comparison between IE and II words would reveal the effect of conflict at just the response level.

Using this logic, Milham et al. (2001) showed in an fMRI study that the ACC is mostly responsive to response-based conflicts (see also van Veen, Cohen, Botvinick, Stenger, & Carter, 2001, who used similar manipulations with the flanker task) whereas a more distributed brain network, including the left prefrontal cortex and the left superior parietal lobule, is responsive to pre-response conflicts. However, Weissman, Giesbrecht, Song, Mangun, and Woldorff (2003), using a cued global/local selective attention task, found that the ACC was not only activated by response conflicts in both the global and the local tasks, but also activated by perceptual and semantic (i.e., pre-response) conflicts arising from global distractors during the local task (also see de Zubicaray, Wilson, McMahon, & Muthiah, 2001). Therefore, it seems that the ACC serves as a general conflict monitoring system, which leads to the recruitment of cognitive control implemented by the DLPFC (Botvinick, Cohen, & Carter, 2004; Botvinick, Braver, Barch, Carter, & Cohen, 2001).

Despite the extensive investigations on the functional roles of the ACC and DLPFC in conflict control, it is not yet clear whether these brain regions will be differentially recruited when the conflict resolution process is modulated by attentional orienting. It has been shown that the magnitude of the Stroop interference effect changes according to whether the Stroop words are presented at a precued or uncued location in exogenous spatial cueing (Vivas & Fuentes, 2001). In this cueing paradigm, an uninformative abrupt onset cue is first presented to attract attention to a peripheral location. A target is then presented either at the cued peripheral location or at the uncued opposite location. Subjects are asked to make a detection or discrimination response to the target. It has been repeatedly found that response to the target at the cued location, compared with response to the target at the uncued location, is delayed if the cue–target stimulus onset asynchrony (SOA) is longer than 300 msec (see Klein, 2000, for a review). This phenomenon is called inhibition of return (IOR), which is often suggested to be a reflexive bias towards novel locations in visual search and orienting (Klein, 2000; Posner & Cohen, 1984). By presenting Stroop words at the cued or uncued location, Vivas and Fuentes (2001) found that the Stroop interference effect was reduced or eliminated at the cued location, suggesting that the cognitive mechanisms underlying the IOR phenomenon interact with the mechanisms underlying the resolution of Stroop interference.

In explaining the reduction of Stroop interference effect at the cued location, Fuentes, Boucart, Vivas, Alvarez, and Zimmerman (2000) and Fuentes, Vivas, and Humphreys (1999) proposed an inhibitory tagging (IT) hypothesis according to which stimuli presented at the cued location are temporally prevented from connecting with their associated response codes. IT applies not only to the task-relevant dimension (i.e., the ink color of the Stroop word) but also to the task-irrelevant (the meaning of the word) dimension. For the incongruent Stroop words, IT interrupts the task-irrelevant word meaning's access to the response system. Thus, response to the color of the incongruent Stroop word would benefit from this disconnection, leading to the reduction of Stroop interference effect at the cued location.

In the present study, we employed the spatial cueing paradigm (Posner & Cohen, 1984), combining the manipulations of IOR and Stroop interference (Vivas & Fuentes, 2001). We differentiated the Stroop interference into pre-response level and response level conflicts following Milham et al. (2001) but put stimuli at either the cued (inhibited) or uncued (noninhibited) locations. Following and Fuentes (2001), we expect that the Stroop interference effect should be affected by IOR behaviorally, with different patterns of effects at the cued and uncued locations. At the neural level, for conflicting information presented *at the uncued location*, the conflict monitoring theory predicts significant ACC activation because of the significant interference effects there. However, because of contradictory findings in previous fMRI studies and because of the suggested general role of the ACC in monitoring conflicting information, it cannot be specifically predicted whether ACC will be activated by the pre-response level conflict, the response level conflict, or both. On the other hand, because the IT hypothesis focuses on the possible IOR mechanism at the cued location, it has no specific predictions for the resolution of conflicting information at the uncued location. For conflicting information presented *at the cued location*, the conflict monitoring theory and IT hypothesis may have different predictions concerning the neural activity in anterior executive brain regions. According to the monitoring theory, when attention is shifted away from the cued location, the conflict between word meaning and the color of stimuli may not be noticed by the 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, Gispen-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.

METHODS

Subjects

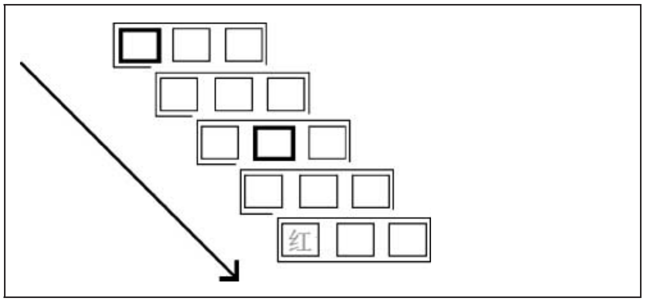
Twelve undergraduate and graduate students (7 women, range 21–29 years) participated in the present study. All of them were right-handed and had normal or corrected-to-normal vision without color blindness or weakness. All the subjects gave written informed consent before scanning and none of them had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

Stimuli and Experimental Paradigm

The experiment had a 2 (cue validity: cued vs. uncued) × 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° of visual angle. Each trial consisted of serial displays (Figure 1) of white boxes presented on a black background. Each box measured 1.5° × 1.5° and the center-to-center distance between two adjacent boxes was 4° 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



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

Data Acquisition

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 × 64, pixel size: $3.4 \times 3.4 \times 5$ 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°). 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 $2 \times 2 \times 2$ mm^3 voxels). The data were then smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate intersubject anatomical variability.

fMRI 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.

RESULTS

Behavioral

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) × 3 (stimulus type) analyses of variance (ANOVAs). Results showed that the main 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).

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.

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.

Imaging

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

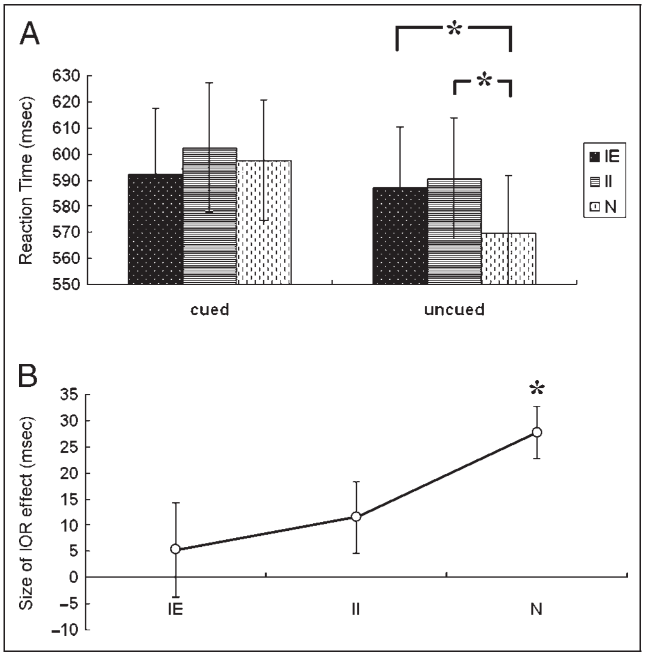


Figure 2. Behavioral results. (A) RTs (msec) with standard errors in the six conditions. (B) The amount of IOR effect (msec) as a function of stimulus type (*the effect reached significance).

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 conflict and the cue validity, that is, "Cued (IE–II) versus Uncued (IE–II)." Thirdly, because the significant IOR effect appeared only on neutral words, we investigated the neural correlates of IOR by comparing neutral words at the cued and uncued locations using an F test on "Cued_N versus Uncued_N."

Table 2 reports all the significantly activated brain regions in the above three F contrasts in terms of peak coordinates, Z score, and extent of activation.

The Interaction between Pre-response Conflict and IOR

The F test "Cued (II–N) versus Uncued (II–N)" was carried out to localize the brain regions responsible for the interaction between the pre-response conflict and IOR. Results revealed a significant cluster of increased neural activity in the left rostral ACC (see Figure 3A). Beta values were extracted from the peak voxel in the activated left rostral ACC cluster and were shown in Figure 3A as a function of the six trial conditions. Beta values in the four conditions involved were highlighted in gray and entered into a 2 × 2 ANOVA. The results demonstrated that the significant interaction between pre-response conflicts and IOR in the left rostral ACC, $F(1,11) = 55.80$, $p < .001$, was because this region showed higher neural activities to II words as compared with neutral words when they were presented at the uncued location, $t(11) = 2.37$, $p < .05$, but it showed a reversed trend when the stimuli were presented at the cued location, $t(11) = 4.90$, $p < .001$.

The Interaction between Response Conflict and IOR

This F test "Cued (IE–II) versus Uncued (IE–II)" was carried out to localize the neural correlates underlying the interaction between response conflicts and IOR. The result revealed a highly significantly activated cluster in the left DLPFC (see Figure 3B). A 2 × 2 ANOVA on the Beta values, extracted from the activation maximum in the left DLPFC and shown in Figure 3B, showed a significant interaction for the four conditions involved, $F(1,11) = 32.85$, $p < .001$. Further analyses showed that this interaction was because the left DLPFC showed higher neural activities to IE words as compared with II words when the stimuli were presented at the cued location, $t(11) = 2.33$, $p < .05$, but the comparison had a reversed pattern when the stimuli were presented at the uncued location, $t(11) = 6.12$, $p < .001$.

We also conducted analyses for the combined pre-response and response conflict effects, treating cue validity (cued vs. uncued) and stimulus type (IE vs. neutral) as two factors in an F contrast. The significantly activated regions were the left DLPFC ($x = -48$, $y = 32$, $z = 19$, 78 voxels), which almost overlapped with DLPFC loci in the above analysis, and the right cerebellum ($x = 34$, $y = -54$, $z = -33$, 84 voxels).

IOR Effect for the Neutral Words

The behavioral data (Table 1 and Figure 2) showed that the significant IOR effect appeared only for neutral words, not for II or IE words. Therefore, F test was carried out to examine neural correlates of the IOR effect for neutral words. This showed significant

Table 2. Brain Regions Activated in the Analyses of Interaction and Cue Validity ($p < .001$, Uncorrected, Extent >60 voxels)

Contrast	*Anatomical Regions*	*Cluster Peak (x, y, z)*	*Z Score*	*Cluster Size (voxels)*
Uncued (II–N) vs. Cued (II–N)	L rostral ACC (BA 32)	−16, 34, 3	4.22	77
Cued (IE–II) vs. Uncued (IE–II)	L middle frontal gyrus (BA 46)	−54, 26, 23	3.72	90
Uncued_N vs. Cued_N	L FEF (BA 6)	−40, 4, 41	4.14	67

Coordinates (x, y, z) correspond to the Talairach atlas (Talairach & Tournoux, 1988).

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 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 processing. Obviously, further studies are needed to test this hypothesis. Although the rostral ACC has been linked to error processing (Kiehl, Liddle, & Hopfinger, 2000) and automatic arousal states (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005) in previous studies, the activation of the rostral ACC for the pre-response conflict at the uncued location in the present study cannot be attributed to these processes. Firstly, although participants may be more alerted to the stimuli at the uncued location, there is no reason to believe that they were alerted differentially to the II and neutral words. Secondly, because participants did not make more errors in the II condition than in the neutral condition at the uncued location and we modeled all the error trials as covariate of no interest in the statistical analysis, error processing cannot be the reason behind the rostral ACC activation for the pre-response conflict effect (''II–Neutral'').

Interaction between Response Conflict and Spatial Attention

The present study suggested that the left DLPFC could be an important neural interface between response level conflicts and spatial attention. Behaviorally, neither IE words nor II words showed significantly slower RTs than neutral words at the cued location, which replicated Vivas et al. (2001). Moreover, the present study extended the finding of Vivas et al. by showing that there was no difference between RTs to IE and II words either (see Figure 2A). Because there was no effect of either pre-response or response level conflict at the cued location behaviorally, one might be tempted to think that there should be no differential activation in the anterior executive brain system when the three types of stimuli were contrasted. Indeed, this could be a prediction made naturally by the general conflict monitoring theory (Botvinick et al., 2001). Although we did not find activation in the ACC, we did, however, observe differential neural responses in the left DLPFC when the contrast between IE and II words (and between IE and neutral words) at the cued location was compared with that at the uncued location. This finding is in agreement 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 (Boetigger 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 temporally disconnecting the S–R association for the task-irrelevant feature.

Indeed, our suggestion is consistent with studies that demonstrated that the DLPFC is a critical brain region underlying inhibitory control (Kelly et al., 2004; Sylvester et al., 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Liddle, Kiehl, & Smith, 2001; Garavan, Ross, & Stein, 1999). However, the executive inhibitory function of the DLPFC explored in these studies was all voluntarily implemented by participants. In other words, participants could experience the interference from incorrect or prepotent responses and they had to voluntarily overcome the interference in the tasks used in previous studies. The present study extended the role of the DLPFC by showing that it also contributes to the unexperienced interference (as indexed by the absence of behavioral interference effect at the cued location) from the task-irrelevant feature.

Neural Correlates of IOR

For neutral words on which significant IOR effects appeared, the left FEF was significantly activated when uncued trials were directly compared with cued trials. This suggests that the left FEF enables human attention system to orient to uncued new spatial locations along the attention shifting path more quickly than to reorient to cued locations.

Previous brain imaging studies on IOR usually defined the neural correlates of IOR by collapsing cued and uncued trials at the long SOA and comparing them with those at the short SOA (Mayer et al., 2004; Lepsien & Pollmann, 2002). These comparisons showed that supplementary frontal eye field (SEF) and the FEF were activated in both cued and uncued trials during IOR (Mayer et al., 2004; Lepsien & Pollman, 2002), a finding interpreted as supporting the oculomotor bias theory of IOR (Taylor & Klein, 1998, 2000; Tassinari, Biscaldi, Marzi, & Berlucchi, 1989; Tassinari, Aglioti, Chelazzi, Marzi, & Berlucchi, 1987). Tassinari et al. (1987, 1989) proposed that IOR is a consequence of maintaining fixation during the experiment. Because the saccade initiated by the peripheral cue has to be suppressed, the motor system is biased against responding to the target at the cued location. These studies, however, did not find significant brain activations for the cue validity effect at long SOAs per se. Mayer et al. (2004) further proposed that because participants cannot predict the location of the upcoming target when the cue is presented, an inhibitory bias should be maintained in both the cued and the uncued trials before the target actually appears. Therefore, the neural substrates responsible for IOR should be commonly activated as a function of SOA for both cued and uncued trials, and brain activities for the cued and uncued trials should be cancelled out when these two are compared directly.

This argument, however, is not completely true because the attentional orienting processes involved in a single trial during IOR include both those induced by the abrupt onset of the spatial cues and those caused by the actual onset of the target. The former may be the same between cued and uncued trials, but the latter should be different according to whether the target was validly cued or not. Participants can orient their attention directly to the uncued target along the attentional shifting path in an uncued trial, but they have to reorient their attention to the cued target subject to IOR in a cued trial. Such difference may cause differential brain activations when cued and uncued trials at the same SOA are compared directly, a comparison more consistent with the classical definition of IOR. Therefore, by the direct comparison between cued and uncued trials 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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