

Functional Dissociation of Attentional Selection within PFC: Response and Non-response Related Aspects of Attentional Selection as Ascertained by fMRI

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In this experiment using a color-word Stroop task, we explored whether different regions of prefrontal cortex bias selection of response-related processes as compared with non-response-related processes. To manipulate demands at the level of response selection, we varied the degree of overlap between stimulus-response mappings in a manual Stroop task. To vary demands at a non-response level, we compared activation for incongruent trials (e.g. the word 'purple' in blue ink) that contain two color representations, one in the word and one in the ink color, to neutral trials (e.g. the word 'drawer' in blue ink), which contain only one color representation, that in the ink color. These manipulations had differential effects within prefrontal cortex. Both a region of right inferior frontal cortex and caudal regions of the cingulate were sensitive to the selection demands at the response-level and insensitive to demands at the non-response level. In contrast, a more anterior region of left dorsolateral prefrontal cortex was sensitive to the number of color representations (i.e. incongruent versus neutral trials), but not to the overlap in stimulus-response mappings. Therefore, this study indicates a functional differentiation for implementing attentional control within prefrontal cortex.

Keywords: attention, color-word Stroop task, non-response selection, prefrontal cortex, response selection

Introduction

The goal of this study was to examine the role of distinct regions of prefrontal cortex involved in attentional control. Here we emphasize the distinction in neural structures that are involved in aiding selection of information that is response-related, as compared with selecting among representations that are not response-related. To do so, we examine neural structures involved in the Stroop task, a classic task of attentional control (MacLeod, 1992). In this task, an individual is asked to pay attention to a word's color while ignoring its meaning or the response to which it leads. Thus, the item's ink color is task-relevant and the meaning of the word (or the response to which it leads) is task-irrelevant. The Stroop task is difficult for a number of reasons. First, there is competition between two processes: word reading and color identification (e.g. Cohen *et al.*, 1990). Because word reading is a more automatic process, cognitive control is required to direct attention to the process of color identification. And the more an item can engender reading related processes (e.g. non-words that follow the rules of English orthography as compared with a string of xxxxxs), the more interference it engenders (Monsell *et al.*, 2001). Second, there can be competition between specific representations contained in Stroop stimuli. For example, reaction times are elongated on incongruent trials (e.g. the word 'red' in blue ink) as compared with neutral trials (e.g. the word 'lot' in blue ink). In incongruent

trials, the meaning of the word provides an alternative color representation to the one contained in ink color. In contrast, in neutral trials, there is only one color representation, that contained in the ink color, as the word has no particular color value. Finally, there can be competition at the response level. For example, in a verbal Stroop task, saying the word 'blue' competes with saying the word 'red'. And in a manual Stroop task, pressing a button associated with one color, such as blue, competes with pressing a button associated with another color, such as red.

Although word reading and color identification processes are in competition for both incongruent and neutral trials, these trials vary with respect to other levels of competition. Incongruent trials are characterized by conflict both with regards to meaning as well as regards to a response, whereas conflict occurs at neither of these levels on neutral trials.

In our prior work, we have suggested that distinct brain regions mediate attentional control for demands engendered at the response level as compared with those involved in attentional demands at the non-response level. Part of our evidence for this assertion comes from studies utilizing a color-word Stroop task in which individuals gave a manual response. In these studies we compared activation for two types of incongruent trials: response-eligible and response-ineligible trials. On response-eligible trials, the word named a potential alternative response (e.g. the word 'red' in blue ink, when red, blue and green are the set of potential responses). In contrast, on response-ineligible incongruent trials, the word does not name a potential alternative response (e.g. the word 'purple' in blue ink, when red, blue, and green are the set of potential responses). We reasoned that regions of the cortex specifically sensitive to response-related attentional demands should exhibit two characteristics. First, they should yield greater activation for response-eligible than response-ineligible trials, since the former should engender response conflict and the latter should not. Second, they should yield no greater activation for response-ineligible trials than neutral trials, since in neither case does the word name an alternative response. In both a hybrid blocked/event-related (Milham *et al.*, 2001) and event-related design (Milham *et al.*, 2003a), the only regions that exhibited such a pattern of activation were contained in the right inferior prefrontal cortex (RIPFC) and the anterior cingulate cortex (ACC). Hence, we argued that these regions are only sensitive to increasing attentional demands at the response level (as exemplified by the conflict between potential responses) but not at the semantic level, since 'purple' identifies a conflicting meaning but does not lead to a conflicting response. In contrast, other regions of dorsolateral prefrontal cortex (DLPFC) exhibited sensitivity to attentional demands at non-response related levels.

In the present study, we provide additional evidence that within prefrontal cortex there are distinct regions involved in response-related aspects of attention from those involved in non-response related aspects of attention. There is one potential objection to the interpretation of our prior results. One might argue that the word on response-eligible trials may be a more potent source of interference not only because it names a competing response, but also because the concept of the color may have been primed by seeing that ink color in the previous trials. For example, if the potential responses (and therefore ink colors) are red, blue, green, processing of the word 'green' may be primed by having seen that ink color on recent trials, making it a strong source of competing information. In contrast, the words used on response-ineligible trials cannot be primed directly by ink color (or not as strongly as those on response-eligible trials), as they never appear as an ink color. Thus, more attentional control may be required on response-eligible than response-ineligible trials because the concept engendered by the word (rather than the response to which it leads) may be a more potent source of interference due to priming across different representations containing color information (i.e. priming from the ink color to a color word). In a recent computational model (Herd *et al.*, in press), we have found that such cross-representational priming influences the Stroop effect.

The present experiment is designed to rule out this alternative explanation for our previous results. One way to do so is to utilize a manipulation of response-related processes that is orthogonal to the color-related representations contained within a stimulus. Hence, we varied the degree of confusability between stimulus-response (S-R) mappings for both incongruent and neutral trials. More specifically, we manipulated number of times a word appeared in a 16-trial block. In some blocks — the four-word blocks — each incongruent word was uniquely paired with one of the four possible ink colors, and each neutral word was uniquely paired with one of the four possible ink colors. Thus, the stimulus-response mapping within condition (incongruent, neutral) was unique. On other blocks — the two-word blocks — two words were shown per condition. In this case, a word could be associated with two colors (e.g. 'brown' in blue ink, 'brown' in red ink; 'table' in blue ink, 'table' in red ink). Finally, in the one-word blocks, each word was paired with each of the four possible colors. Thus, the stimulus-response mappings overlapped to the greatest degree on the one-word blocks (one word associates with four possible buttons) and the least on the four-word blocks (each word associates with one button).

If the regions we have previously identified as being response-related are indeed involved in selection at response-related levels, then they should exhibit greater activation on one- than four-word blocks due to the greater overlap between competing stimulus-response mappings. This effect should be observed regardless of whether the word is neutral or incongruent with ink color, as it should not be affected by conflict at non-response levels (i.e. whether the concept blue interferes with the concept of red). To preclude the possibility that the word's meaning could be primed by ink color, we restricted our stimuli to response-ineligible trials in the present experiment.

We predict that we will observe a dissociation between those regions of prefrontal cortex that are sensitive to the manipulation of stimulus-response mappings (i.e. one- versus two-, versus four-word blocks) as compared with those sensitive to the manipulation of competition at non-response levels (i.e. incongruent versus neutral trials). Based on our prior results, we

predict that regions of right inferior frontal cortex and the anterior cingulate should be sensitive to overlap in stimulus-response mappings, but not to non-response related conflict as instantiated in the contrast between incongruent and neutral trials. In contrast, we hypothesize that more dorsolateral regions of prefrontal cortex should be sensitive to non-response related demands, but not to response-related demands.

Materials and Methods

Participants

Fourteen right-handed, native English speakers (age range 24–40 years; eight women) were recruited from the local community. All participants had normal or corrected to normal vision and none were colorblind. A signed informed consent form approved by Colorado Multiple Institutional Review Board was obtained from each participant prior to the experiment.

Stimuli

Stimuli were color words (e.g. 'purple') and furniture words (e.g. 'drawer'), printed in one of the four different ink colors (i.e. blue, green, red and yellow), as well as strings of white plus signs that varied in length from three to six (see Fig. 1A). Half of the words were incongruent (e.g. the word 'purple' in blue ink) whereas the other half were neutral (e.g. the word 'drawer' in blue ink). On incongruent trials, the word never named one of the possible responses (i.e. the words 'blue', 'red', 'green', and 'yellow' were excluded). Seven distinct incongruent words were utilized as well as seven neutral words. They were matched as closely as possible for word length and frequency. This allowed the words in each of the repetition conditions to be unique. Furthermore, because all the color words are semantically related, we made the neutral words semantically related as well (e.g. they are exemplars of furniture). The participants were asked to identify the ink color of the colored stimuli via a four-choice button press as accurately and quickly as possible, while ignoring the meaning of the colored stimuli.

Design

We employed a 2 × 3 factorial design. The two factors were: (i) whether the word named a conflicting color; and (ii) the overlap of stimulus-response mappings. To vary conflict at non-response levels, we utilized two types of trials: incongruent color words (I) and neutral words (N). On incongruent trials the color described by the word conflicted with

A

| Fixation | Incongruent 1-word | Neutral 1-word | Incongruent 2-word | Neutral 2-word | Incongruent 4-word | Neutral 4-word |
|----------|--------------------|----------------|--------------------|----------------|--------------------|----------------|
| +++++ | purple | drawer | brown | table | orange | window |
| ++++ | purple | drawer | pink | sofa | violet | closet |
| +++ | purple | drawer | brown | table | cyan | door |
| ++ | purple | drawer | pink | sofa | tan | bed |

B

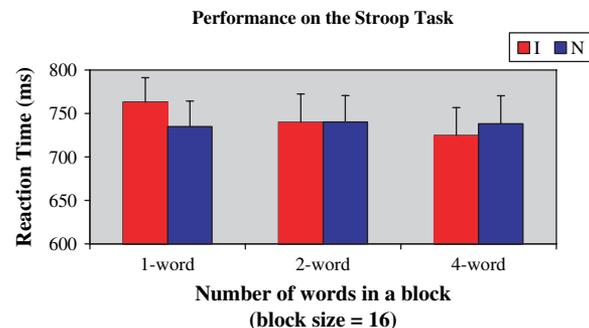


Figure 1. (A) Stimuli used for each of the conditions. (B) Reaction times for the one-, two- and four-word blocks for incongruent (I) and neutral (N) trials. Responses to one-word incongruent trials are significantly slower than those to one-word neutral trials and four-word incongruent trials.

the item's ink color, whereas on neutral trials, the word had no color-related meaning and hence did not provide a source of conflict. To vary the overlap of stimulus-response mappings, we varied the number of different words used within a block (one, two and four words). For all three conditions, words appeared in the same four ink colors. For example, in the one-word condition, although only one word was viewed (e.g. 'purple' or 'drawer'), it was paired with each of the four ink colors. In the two-word condition, two different words in both the incongruent and neutral conditions were presented, each paired with two ink colors. In the four-word condition, each of four other distinct words was paired with one of the four ink colors. Thus, all three conditions involved four unique color-word pairs, controlling for the frequency of color-word combinations. Six different conditions were created by crossing these two factors (I1, N1, I2, N2, I4 and N4).

Procedures

A boxcar design was implemented with each run consisting of three incongruent blocks (I1, I2 and I4) and three neutral blocks (N1, N2 and N4), with a fixation block at the beginning and the end of each functional run. The fixation condition consisted of letter strings of three to six white plus signs (comparable to the length of words used), which individuals viewed passively without making a response. Incongruent and neutral blocks containing similar number of words were presented contiguously. Each block consisted of 16 trials, with each trial lasting 2500 ms (300 ms of a black cross, 1500 ms of stimulus presentation and 700 ms of inter-stimulus interval), for a total of 135 trials per run. Each participant completed three runs. The order of frequency blocks (one-, two- and four-word) was counterbalanced across three runs, while the order of incongruent and neutral blocks was counterbalanced across participants.

Data Acquisition

A 1.5 T Siemens Vision magnetic resonance imaging system located at the University of Colorado Health Sciences Center equipped for echo-planar imaging (EPI) was used for data acquisition. EPI images were acquired using the BOLD technique ($T_R = 2500$ ms, $T_E = 40$ ms, flip angle = 90°), each consisting of 20 contiguous axial slices (matrix = 64×64 , in-plane resolution = 3.75×3.75 mm², thickness = 6 mm, gap = 0.9 mm), parallel to the anterior commissure-posterior commissure line. Prior to the EPI images, a high-resolution T1-weighted MPRAGE (magnetization prepared rapid gradient echo) anatomical set (168 coronal slices of full head, matrix = 256×256 , field-of-view = 250×250 mm², slice thickness = 1.5 mm, no gap) was collected for each participant. At the end of the experiment, a T1-weighted spin echo data set (20 axial slices, matrix = 512×512 , field-of-view = 230×230 mm², slice thickness = 6 mm, gap = 0.9 mm) was acquired using the same slice angles as the EPI images.

Stimuli were presented using a high-resolution rear projection system with responses recorded via a fiber-optics response pad with four buttons. A laptop computer running E-Prime controlled stimulus presentation and the recording of responses. In addition, the timing of the stimulus presentation was synchronized with trigger pulses.

Image Pre-processing

Prior to statistical analysis, the first seven volumes of each run were discarded to allow the MR signal to reach steady state. The remaining images in each participant's time series were motion corrected using the MCFLIRT module of FSL (FMRIB's Software Library, v3.1) package (<http://www.fmrib.ox.ac.uk/fsl>). Images in the data series were then spatially smoothed with a 3D Gaussian kernel (full-width half-maximum = $8 \times 8 \times 8$ mm³), and temporally smoothed using a high-pass filter (1.5 repetition cycle). The FEAT (FMRIB's Expert Analysis Tool) module of FSL package was used for these steps and later statistical analysis.

Analysis on Individual Participant

First, customized square waveforms for each participant were generated for the individual's specific counterbalanced order of experimental conditions. These waveforms were convolved with a double gamma hemodynamic response function (HRF). For each participant, we used FILM (FMRIB's Improved Linear Model) to estimate the hemodynamic parameters for the different explanatory variables (EVs; e.g. one for incongruent Stroop condition and another for neutral condition) and

generate statistical contrast maps of interest (e.g. a contrast between EVs for incongruent and neutral conditions).

After statistical analysis for each subject's time series, contrast maps were warped into common stereotaxic space before mixed-effects group analyses were performed. This involved registering average EPI image to the T1 spin echo image, then to the MPRAGE image, and finally to the ICBM152 T1 template, using FLIRT (FMRIB's Linear Image Registration Tool) module of FSL package.

Mixed-effects Group Analysis

Contrast maps of parameter estimates (PE) were transformed into a common stereotaxic space using the above-mentioned three-step registration prior to the group analyses with FLAME (FMRIB's Local Analysis of Mixed Effects).

Region of Interest (ROI) Analysis

To identify the regions of brain activation, we defined the ROIs first by clusters of 30 or more contiguous voxels (Xiong *et al.*, 1995) in which PE values differ significantly from zero ($Z > 2.81$ $P < 0.005$ two-tailed). Using Mintun peak algorithm (Mintun *et al.*, 1989), we further locate the local peaks (maximal activation) within each ROI. We also examined whether the main effects that were identified for the ROI analysis held for each of the pairwise comparisons of interest. For example, for the peaks that were identified as being significantly more active for incongruent than neutral trials, we then tested each of the pairwise conditions separately that made up this contrast (e.g. I1 versus N1, I2 versus N2, I4 versus N4), using the average extracted PE values of a $3 \times 3 \times 3$ cube centered on the peak voxel of each ROI.

Results

Behavioral Data

The effects of incongruency and repetition frequency of words on the reaction time and accuracy of the Stroop task were tested using repeated-measures analyses of variance (ANOVAs) with the factors of Trial Type (I and N) and Condition (one-, two- and four-word).

Reaction Time

The average reaction times for the cells of trial type by repetition condition are shown in Figure 1B. Although there were no main effects of either factor, the interaction between the two factors was significant, $F(2, 26) = 3.87$, $P < 0.05$. Post-hoc Newman-Keuls paired comparisons indicated that there were no significant differences in RT among the three neutral conditions (one-, two- and four-word). Participants responded significantly more slowly to the I1 condition ($M = 763$ ms) than to both I4 ($M = 725$ ms) and N2 condition ($M = 740$) ($P < 0.025$). There was also a trend for slower responses to the I1 condition than to the I2 ($M = 740$ ms) and N1 ($M = 735$) conditions ($P < .10$). These findings suggest that greater overlap of stimulus-response mappings was associated with slower reaction time. They also suggest that incongruent trials are associated with greater attentional demands than neutral trials. Because of the effects of trial type and repetition condition interacted, in our imaging data we tested not only the main effect of interest (e.g. the degree of S-R mappings overlap), but also examined whether such an effect held individually for each level of the other main factor (e.g. the effect of S-R mappings overlap for incongruent trials only, the effect of S-R mappings overlap for neutral trials only).

Accuracy

No significant differences across conditions were observed. The overall average accuracy was 96%. Only one participant's

average accuracy fell below 90% (77%). However, his accuracy did not differ across different experimental conditions.

Imaging Data

Areas Sensitive to Conflict between the Ink Color and Word

As an initial step, we examined those brain regions that exhibited greater activation for incongruent than neutral trials to determine how well they agree with results from our prior studies. The results accord well with our previous studies. Frontal areas activated include regions of the left middle and inferior frontal gyrus [including Brodmann area (BA) 9 and BA 44], as well as the left inferior parietal lobe (BA 40). We also obtain activation in the left middle and superior temporal gyrus (bordering on supramarginal gyrus BA 22) as well as the lingual gyrus (see peaks listed in Table 1). The effects are more robust for the I4 versus N4 contrast (the contrast that is most analogous to our prior studies) than the I1 versus N1 contrast. In fact, when restricted to the one-word condition, the left inferior frontal region does not yield a significant effect. This finding is consistent with our prior studies showing that these regions tend to decrease in activation with practice (Milham *et al.*, 2003b).

Of most importance to our hypothesis, activation for this contrast was observed in regions of DFLPC (along with inferior frontal gyrus in the left hemisphere). Furthermore, as can be seen in Table 1, tests on the peaks in this region indicate that they are not significantly more activated for the one- than four-word blocks. This finding indicates that these regions are relatively insensitive to the overlap in stimulus-response mappings. The regions observed in the current study also overlap with what we observed in our prior study comparing activation for rare incongruent trials as compared with rare neutral trials (Milham *et al.*, 2003a).

Areas Sensitive to Repetition Frequency of Words and Degree of Overlap between Stimulus-Response Mappings

In an attempt to find a linear relationship between the brain activation and the overlap between stimulus-response mappings, we had varied the number of words parametrically across blocks. However, our initial analyses did not reveal such a parametric relationship (e.g. the two-word condition did not systematically yield a pattern of activation significantly different from both the one- and four-word conditions). Thus, to maximize our ability to detect effects of the contrast of interest, we revised our analysis to compare only the most disparate conditions,

the one- and four-word conditions, isolating those regions that exhibited greater activity to the one-word condition with the highest degree of stimulus-response overlap, as compared with the four-word condition with the least degree of stimulus-response overlap. Three different types of brain regions were identified in this contrast: those related to attentional control, those related to visual processing, and those related to language processing (see Table 2).

Attention-related Areas. We observed activation in a variety of regions in the fronto-parietal network that are important for top-down attentional control. We also observed activity in the anterior cingulate regions that we have found to be related to selection at response-related stages. None of these regions exhibits significantly greater activity to incongruent than neutral trials.

Activation was observed in right middle (BA 46 and ventral BA 9) and inferior frontal gyrus (BA 44/45). Furthermore, these regions do not show significant increased activation for incongruent relative to neutral trials. In our prior studies with the Stroop task we have usually obtained activation in left DLPFC, with additional regions of right DLPFC as attentional demands increase (Banich *et al.*, 2000a,b; Milham *et al.*, 2002).

We obtained activity in the right inferior parietal lobe and precuneus, both of which are regions that we have observed previously to be activated in the Stroop task. A peak within the inferior parietal lobule in BA 40 is in a region that has been identified as being involved across various tasks requiring visual attention (Wojciulik and Kanwisher, 1999). It has been suggested that this area may be involved in suppressing task-irrelevant distractors (Wojciulik and Kanwisher, 1999, *P.* 758). There is also a region activated in the precuneus, which has been linked to visual processing and attention (Culham and Kanwisher, 2001).

Two regions of anterior cingulate cortex were identified, one in the right hemisphere and one in the left. These regions extended from just above the callosum to the border of the cingulate gyrus into the supplementary motor area. We have found that these regions are activated when selection at the response-related stages of processing gets difficult (Milham *et al.*, 2001, 2003a; Milham and Banich, 2005).

Visual Processing Regions. We observed activity in a variety of visual processing regions suggesting that indeed the physical representation of the word was enhanced by repeated presentation.

We observed greater activity in primary and second visual cortex (BA 17, 18, 19), regions that have previously been

Table 1

Peaks within regions that exhibited significantly greater activity for incongruent as compared with neutral trials, across the blocks

| Label | BA | Peaks ^a | I1 versus N1 | I4 versus N4 | I1 versus I4 | N1 versus N4 |
|----------------------------|----|--------------------|--------------|--------------|--------------|--------------|
| L middle frontal gyrus | 9 | -54, 22, 30 | 0.006** | 0.002** | 0.167 | 0.228 |
| R superior frontal gyrus | 10 | 34, 64, 12 | 0.046* | 0.011* | 0.696 | 0.679 |
| L inferior frontal gyrus | 44 | -52, 16, 16 | 0.177 | 0.008** | 0.136 | 0.998 |
| L inferior parietal lobule | 40 | -40, -60, 40 | 0.035* | 0.012* | 0.478 | 0.725 |
| L superior temporal gyrus | 22 | -40, -52, 20 | 0.049* | 0.082 | 0.776 | 0.642 |
| L middle temporal gyrus | 21 | -60, -48, -8 | 0.002** | 0.022* | 0.885 | 0.697 |
| L lingual gyrus | 18 | -6, -100, -14 | 0.114 | 0.001*** | 0.578 | 0.607 |

The *P* values for the significance of specific simple contrasts are provided in each of the four right hand columns.

^aCoordinates are in MNI space.

P* < 0.05; *P* < 0.01; ****P* < 0.001.

Table 2

Peaks within regions that exhibited significantly greater activity for one-word blocks as compared with four-word blocks, across the incongruent and neutral trials

| Label | BA | Peaks ^a | I1vN1 | I4vN4 | I1vI4 | N1vN4 |
|----------------------------|----|--------------------|--------|-------|----------|----------|
| Attention | | | | | | |
| R middle frontal gyrus | 46 | 36, 40, 12 | 0.894 | 0.364 | 0.008** | 0.016* |
| R inferior frontal gyrus | 45 | 50, 24, 26 | 0.374 | 0.083 | 0.035* | 0.005** |
| R inferior frontal gyrus | 44 | 54, 10, 16 | 0.479 | 0.714 | 0.000*** | 0.005** |
| R inferior frontal gyrus | 45 | 48, 28, 8 | 0.854 | 0.381 | 0.005** | 0.002** |
| R anterior cingulate gyrus | 32 | 4, 22, 40 | 0.632 | 0.937 | 0.008** | 0.005** |
| L anterior cingulate gyrus | 24 | -8, 4, 36 | 0.205 | 0.617 | 0.039* | 0.021* |
| R inferior parietal lobule | 40 | 36, -46, 54 | 0.354 | 0.686 | 0.005** | 0.000*** |
| R precuneus | 7 | 8, -62, 54 | 0.521 | 0.668 | 0.006** | 0.018* |
| Visual | | | | | | |
| Calcarine | 17 | 0, -94, 0 | 0.249 | 0.839 | 0.004** | 0.090 |
| Cuneus | 18 | 0, -94, 28 | 0.014* | 0.304 | 0.002** | 0.003** |
| R middle occipital gyrus | 18 | 28, -80, 10 | 0.208 | 0.143 | 0.120 | 0.000*** |
| R fusiform gyrus | 19 | 30, -70, -20 | 0.888 | 0.894 | 0.063 | 0.009** |
| Language | | | | | | |
| R superior temporal gyrus | 41 | 48, -38, 16 | 0.565 | 0.997 | 0.001*** | 0.030* |
| L superior temporal gyrus | 42 | -52, -36, 16 | 0.429 | 0.909 | 0.000*** | 0.006** |
| R middle temporal gyrus | 21 | 48, -20, -6 | 0.996 | 0.764 | 0.001** | 0.000*** |
| L middle temporal gyrus | 21 | -52, -40, -2 | 0.148 | 0.070 | 0.024* | 0.007** |
| L middle temporal gyrus | 37 | -50, -56, 6 | 0.051 | 0.347 | 0.005** | 0.224 |
| Other | | | | | | |
| Sub-gyral | 37 | -32, -30, 0 | 0.763 | 0.574 | 0.009** | 0.024* |
| Sub-gyral | 21 | 44, -54, 2 | 0.629 | 0.611 | 0.008** | 0.206 |
| Sub-gyral | | 40, 0, -22 | 0.575 | 0.406 | 0.017* | 0.025* |
| Cerebellar | | 28, -40, -42 | 0.776 | 0.187 | 0.011* | 0.004** |
| Cerebellar | | 22, -54, -44 | 0.130 | 0.677 | 0.001*** | 0.003** |
| Cerebellar | | -22, -80, -38 | 0.365 | 0.245 | 0.084 | 0.052 |
| Mid-brain | | -2, -22, -16 | 0.467 | 0.597 | 0.000*** | 0.000*** |

The *P* values for the significance of specific simple contrasts are provided in each of the four right hand columns.^aCoordinates are in MNI space.**P* < 0.05; ***P* < 0.01; ****P* < 0.001.

suggested to be involved in perceptual priming (Vaidya *et al.*, 1998; Badgaiyan, 2000). We suggest that these regions represent the priming of visual representations of the word's form. Consistent with this conjecture is that one peak of activity in our study [$x = 3, y = -70, z = -22$] is similar to that observed in the contrast of activation for viewing words as compared with false fonts (Brunswick *et al.*, 1999). Activity is also observed in regions that have previously been found to be activated when viewing single words as compared with fixation points (Petersen *et al.*, 1988; [$x = 6, y = -72, z = 10$]).

Language-related Areas. Activity was observed in many classical language related regions, suggesting that with increased repetition the word is better able to prime language-related representations.

Superior temporal gyrus (STG) activation was observed in both hemispheres, with large left-sided activation spanning from BA 37 up into angular gyrus coupled with less extensive right-sided activation. One peak within BA 42 of the left hemisphere [$x = -52, y = -36, z = 16$] is a region that has been implicated both in phonological (Price, 2000; Haist *et al.*, 2001) as well as semantic processing (Chee *et al.*, 2003) of words. The more dorsal activation into the angular gyrus has been linked to extracting meaning from written form (Price, 2000).

Bilateral activation was observed in the middle temporal gyrus (MTG, BA 21). A posterior region in left MTG (BA 37) is the only one that shows significant activation for the I1 versus I4 contrast, but not for the N1 versus N4 contrast. We suggest that these regions may specifically be processing the semantics of the word, consistent with the suggestions of Price (Price, 2000). Only incongruent trials contain words that are color-related whereas neutral words do not. Hence, we believe this increased

activation for the I1 versus I4 contrast reflects the increased priming of the semantic representation of a single incongruent color word, making it a more potent source of interference with identification of the ink color.

ROI Analysis

Because of theories that differentiate the role of DLPFC and ACC in cognitive control (e.g. Botvinick *et al.*, 2001), we wished to examine more carefully the dissociation between regions in left DLPFC that yielded significant activation for non-response related information (i.e. incongruent versus neutral trials), as compared with regions in RIPFC and ACC that were sensitive to response-related processing. First, we confirmed that a cube ($3 \times 3 \times 3$ voxels) centered on the peak in left DLPFC was only significantly active for the contrast of incongruent versus neutral trials, but not for the contrast of one-word versus four-word blocks (see Fig. 2A). Second, we confirmed that the opposite pattern, namely significant activation for the one-word versus four-word contrast but not for the incongruent versus neutral contrast, was observed in RIPFC and ACC (see Fig. 2B).

Therefore left DLPFC, as compared with RIPFC and ACC, showed separate modifiability, a property signified by distinct mental modules as proposed by Sternberg (2001). As a stronger test, we performed ANOVA tests comparing the effects of these manipulations for the regions of interest. An ANOVA with the factors of trial types (incongruent versus neutral), overlap of S-R mappings (one- versus four-word), and regions of interest (left DLPFC versus RIPFC) was performed on the parameter estimates for these peaks (average of the 27 voxels in the cubes). It yielded a significant two-way interaction between the regions and trial types [$F(1,13) = 8.09, P = 0.014$] as well as an interaction between the regions and overlap of S-R mappings

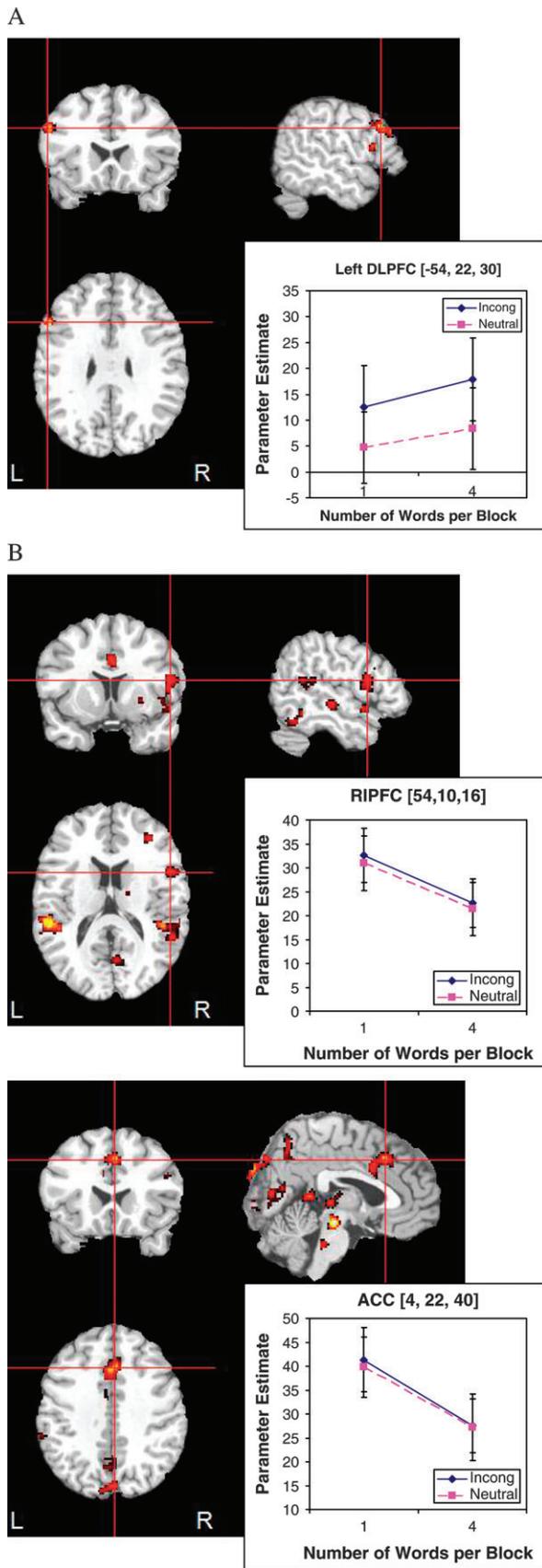


Figure 2. (A) A region of left DLPFC that exhibits significantly greater activity for incongruent than neutral trials. (B) Regions of RIPFC and ACC that exhibit significantly greater activity for one-word blocks than four-word blocks.

[$F(1,13) = 18.72, P = 0.001$]. A similar ANOVA comparing the regions of left DLPFC and ACC also yielded a significant two-way interaction between the regions and trial types [$F(1,13) = 7.18, P = 0.019$] as well as an interaction between the regions and overlap of S-R mappings [$F(1,13) = 12.79, P = 0.003$].

Discussion

The results of the present experiment provide support for the idea that a functional distinction exists within prefrontal cortex between regions involved in selection that is response-related as compared with selection that is not response-related. In particular, we found that RIPFC and ACC exhibited significantly greater activity when there was greater overlap of stimulus-response mappings as compared with when these mappings were unique. Of note, the activity of these regions were not significantly modulated by whether the trial was incongruent or neutral. In contrast, activity of a more anterodorsal region of left DLPFC was greater for the incongruent than neutral trials. Since we used the response-eligible incongruent trials in the current study, we could ensure that the greater need for attentional control on incongruent trials was engendered at non-response-related levels of processing. Furthermore, activity of this region was insensitive to selection demands engendered by overlap of stimulus-response mappings. A formal contrast showed a dissociation in the activation patterns between these regions. Thus, the present results are important as they provide evidence of a double dissociation in the nature of attentional control implemented in these subregions of prefrontal cortex.

The results of the present study are consistent with prior work performed in our laboratory. Using both a hybrid blocked/single trial design (Milham *et al.*, 2001) and an event-related design (Milham *et al.*, 2003a), we have found a region of right inferior frontal cortex almost identical to that identified in the current study to be specifically linked to response-related processes. In those studies, this region exhibited greater activity to the response-eligible than response-ineligible incongruent trials. However, in those studies there existed the logical possibility that the ink color in prior trials could potentially prime the meaning of the related color word, making the word a more potent source of interference. The current study, however, rules out the possibility that the activity of right prefrontal regions was driven by such a mechanism, as all the incongruent trials in the present experiment were of the response-ineligible variety. In addition, the region of left DLPFC that was identified as yielding more activity to the incongruent than neutral trials is quite similar to those found by Milham *et al.* (2003a). What we have demonstrated is a dissociation, in that each of these areas is sensitive only to selection demands at one level (e.g. response-related) but not another (e.g. non-response-related).

The findings of the current experiment are also consistent with other findings in our laboratory (Jacobson, 2005). In that study, individuals were trained on specific word-color pairs (e.g. 'blue' in red ink, 'yellow' in green ink). During two subsequent blocks of test sessions, they received either the identical trials as during training or re-pairings of the same word and the same colors (e.g. 'blue' in green ink, 'yellow' in red ink). One contrast from that study is highly relevant to the present results. This contrast specifically examines the effect of the introduction of additional stimulus-response mappings. It contrasts activation for identical trials during training, when there is only one set of stimulus-response mappings, to those same trials, in the first

block of testing, when an additional set of stimulus–response mappings have been introduced by the re-paired trials. Greater activation was observed for the latter condition in the same right inferior prefrontal cortex as in the current study.

We also have converging evidence that the increased activation of anterodorsal regions of left DLPFC to the incongruent as compared with neutral trials is driven by the fact that there are two color-related representations on the incongruent trials. One might consider the alternative explanation that the increase is driven by the fact that the representations are conflicting on the incongruent trials while they are not on the neutral trials. However, we have observed similar activity of anterior DLPFC whenever the stimulus contains two color-related representations, both when these representations conflict as on the incongruent trials, and when they do not as on the congruent trials (e.g. the word ‘red’ in red ink) (Milham *et al.*, 2002; Milham and Banich, 2005). Congruent trials, like incongruent trials, contain two color-related representations — one contained in the word and the other contained in the ink color.

The present data also provide some indirect evidence that it is the number of color-related representations that is driving activity of anterodorsal DLPFC. This tentative evidence is revealed not by a consideration of how many color representations exist for a given trial as we have emphasized throughout most of this paper, but rather by a consideration of how many color-related representations exist within a block. The activation in left anterodorsal DLPFC is more robust for the I4 versus N4 contrast than the I1 versus N1 contrast, although it should be noted that no significant interaction exists (see Table 1). Across a block of trials in the one-word incongruent condition, there are a total of five color-related representations, one color word plus four ink colors. In contrast, in the four-word incongruent condition, there are a total of eight color related representations, four color words and four ink colors. Notice that although there are also more words in the N4 than N1 condition, the number of color-related representations stays constant, at four ink colors. Thus, the suggestion of a slightly more robust effect for the I4 versus N4 contrast than that observed for the I1 versus N1 contrast in anterodorsal DLPFC may reflect the increased number of color representations encountered in the I4 relative to I1 condition.

The data in the present study also shed some light on the debate in the literature about the relative roles of the DLPFC and ACC in attentional control. We have argued that ACC is mainly involved in response-related processes (Milham *et al.*, 2001, 2003a; Milham and Banich, 2005) with DLPFC taking a lead role in top-down attentional control (Milham *et al.*, 2003b). This contrasts with other viewpoints suggesting that the role of ACC is to detect conflict, and then in turn signal a need for increased attentional control (Botvinick *et al.*, 2001). Proponents of this latter viewpoint have pointed to results from several studies in which they have examined activation in the ACC as a function of the previous trial type to argue against the ‘selection-for-action’ role of ACC (Botvinick *et al.*, 1999; Carter *et al.*, 2000; Kerns *et al.*, 2004). For example, Botvinick *et al.* (1999) used a flanker task in which they asked participants to respond to the direction of the central arrow, which was surrounded by either congruent (C) or incongruent (I) distractors. They found that activity of the ACC was the greatest to incongruent trials that had been preceded by a congruent trial (i.e. CI pairings). In contrast, activity of the ACC was attenuated when incongruent trials were preceded by an incongruent trial (i.e. II pairings). The amplitude of response to these trials was

similar to that of the remaining conditions (e.g. CC and IC pairings). The authors argued that conflict was greater on incongruent trials preceded by a congruent trial (the CI pairings) than those preceded by an incongruent trial (the II pairing) because the previous congruent trial did not contain conflict. Hence, the ACC was not activated to intervene to resolve the conflict. On the other hand, when the previous trial was incongruent, the ACC detected conflict and signaled the DLPFC that greater attentional control was needed. According to this account, the greater control exerted by the DLPFC lessens the conflict on the subsequent incongruent trial.

However, from the standpoint of the critical trial in the pair, which is the second item — the incongruent trial — one could argue that there is no more conflict whether it is preceded by a congruent or incongruent trial. The conflict is engendered equally on those trials because the target and distractors always point in the opposite directions. Rather, it is the selection-for-action of the prior trial that matters. Due to the greater need for selection-for-action in the previous incongruent trial, the ACC is already activated and working efficiently. There is no need to further ramp up activity of ACC to enhance the selection process for the following incongruent trial. This priming related attenuation of brain activity has been documented for other brain regions (see reviews in Grill-Spector and Malach, 2001; Henson, 2003). In contrast, to select the correct response, the ACC must ramp up activity for an incongruent trial when it has been relatively inactive following a congruent trial.

The results of the present study are consistent with our theorizing that activity of the cingulate is very sensitive to response-related factors, and not specific to conflict monitoring *per se*. We observed no ACC activation in the contrast of the incongruent versus neutral conditions. Of importance, we utilized response-ineligible incongruent stimuli, in which the word did not name a potential response. Hence, these trials would only engender conflict at a pre-response level (e.g. at a semantic level) but not at response-related stages of processing. van Veen *et al.* (2001) also found in a flanker task that the conflict at perceptual level alone did not elicit significant activation of the ACC and suggested that it may be involved in the response related level of processing. In contrast, the greater conflict engendered at the response level, due to the stimulus–response mapping ambiguity in the one- as compared with four-word conditions, significantly activated the ACC. A similar pattern of activation was observed for right inferior prefrontal regions. In prior studies, we have also observed that activation of RIFPC and caudal regions of ACC often co-occur, suggesting a functional linkage (see Milham and Banich, 2005). What is not directly addressed in the present study is a possible differentiation of function between these two regions.

In sum, the present study provides evidence that distinct regions of prefrontal cortex are involved in response-related versus non-response-related aspects of attentional control. On the basis of our findings, we propose that anterodorsal regions of left DLPFC aid in non-response aspects of selection. In contrast, right inferior prefrontal cortex in concert with caudal regions of anterior cingulate cortex aid in response-related aspects of selection.

Notes

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