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Reactive Mechanism of Cognitive Control System

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The prefrontal cortex (PFC) is thought to modulate the neural network state in favor of the processing of task-relevant sensory information prior to the presentation of sensory stimuli. However, this proactive control mechanism cannot always optimize the network state because of intrinsic fluctuation of neural activity upon arrival of sensory information. In the present study, we have investigated an additional control mechanism, in which the control process to regulate the behavior is adjusted to the trial-by-trial fluctuation in neural representations of sensory information. We asked normal human subjects to perform a variant of the Stroop task. Using functional magnetic resonance imaging, we isolated cognitive conflict at a sensory processing stage on a single-trial basis by calculating the difference in activation between task-relevant and task-irrelevant sensory areas. Activation in the dorsolateral PFC (DLPFC) covaried with the neural estimate of sensory conflict only on incongruent trials. Also, the coupling between the DLPFC and anterior cingulate cortex (ACC) was tighter on high-sensory conflict trials with fast response. The results suggest that although detection of sensory conflict is achieved by the DLPFC, online behavioral adjustment is achieved by interactive mechanisms between the DLPFC and ACC.

Keywords: anterior cingulate cortex, conflict, dorsolateral prefrontal cortex, functional magnetic resonance imaging, single-trial analysis

Introduction

Goal-directed behavior requires selection of task-relevant information and suppression of task-irrelevant information. This is shown to be mediated by control signals from the prefrontal cortex (PFC), which proactively biases the state of brain network in favor of the processing of task-relevant information (Desimone and Duncan 1995; Kastner and Ungerleider 2000; Miller and Cohen 2001; Corbetta and Shulman 2002; Morishima et al. 2009). The demand of cognitive control increases when task-irrelevant information competes with task-relevant information. In an experimental setting such as the Stroop or Flanker task, behavioral response slows down on incongruent trials in which task-relevant and task-irrelevant information can lead to different behavioral responses than on congruent trials in which task-relevant and task-irrelevant information lead to the same behavioral response (MacLeod 1991; Gratton et al. 1992). In such situations, an optimal state of the brain network in favor of the processing of task-relevant information is thought to be achieved by the proactive control mechanism. However, an optimal network state cannot always be established due to intrinsic fluctuations of neural activity: The same sensory information, even in the same task condition, can cause different levels of neural activation across trials. In the context of cognitive conflict, such fluctuation creates different levels of conflict between neural representations of task-relevant and task-irrelevant sensory information. Thus, an additional mechanism of reactive control is required to regulate behavior upon arrival of actual sensory information (Braver et al. 2003; Bunge 2004). Its precise neural mechanism, however, remains open because of the difficulty in estimating the level of conflict at a sensory processing stage on a trial-by-trial basis.

In the present study, we have conducted single-trial analysis of the fluctuation in the level of conflict at a sensory processing stage. To this end, we used functional magnetic resonance imaging while normal human subjects performed a variant of Stroop task (Fig. 1*A*). We estimated the level of conflict between competing sensory information on a single-trial basis by calculating the difference in brain activation between task-relevant and task-irrelevant sensory areas. We considered that the cognitive control system adjusts itself according to the level of the sensory conflict and regulates behavior online. Consistent with the idea, we found that the dorsolateral prefrontal cortex (DLPFC) was highly active on high-sensory conflict trials compared with low-sensory conflict trials, but this was observed only on incongruent trials, not on congruent trials, suggesting that the DLPFC detects sensory conflict that needs to be resolved for the current behavioral goal. We also found tighter coupling between the DLPFC and anterior cingulate cortex (ACC) resulted in faster behavioral response on trials with high-sensory conflict. Taken together, we present a comprehensive account of the neural mechanism involved in online adjustment of cognitive control.

Materials and Methods

Subjects

Sixteen healthy right-handed adults (8 females; aged 20–38) participated in the experiments. One subject was excluded from the analysis due to a hardware problem. All subjects gave written informed consent to participate in this study. The study was approved by the ethics committees of the Graduate School of Medicine, the University of Tokyo and the Brain Science Institute, Tamagawa University.

Tasks

Subjects performed a cued Stroop task for face and word stimuli. These stimuli were used to take advantage of object-specific activation in the fusiform face area (FFA) (Kanwisher et al. 1997) and visual word form area (VWFA) (Cohen et al. 2000), which respond to a face image and word, respectively. The subjects were first presented with a task instruction cue followed by a target stimulus on the black background. The target stimulus was a gray face image of a male or female (Softopia Japan Foundation, Gifu, Japan) superimposed with a "kanji" letter, a Japanese ideogram, representing a male or female (Fig. 1*A*). The visual

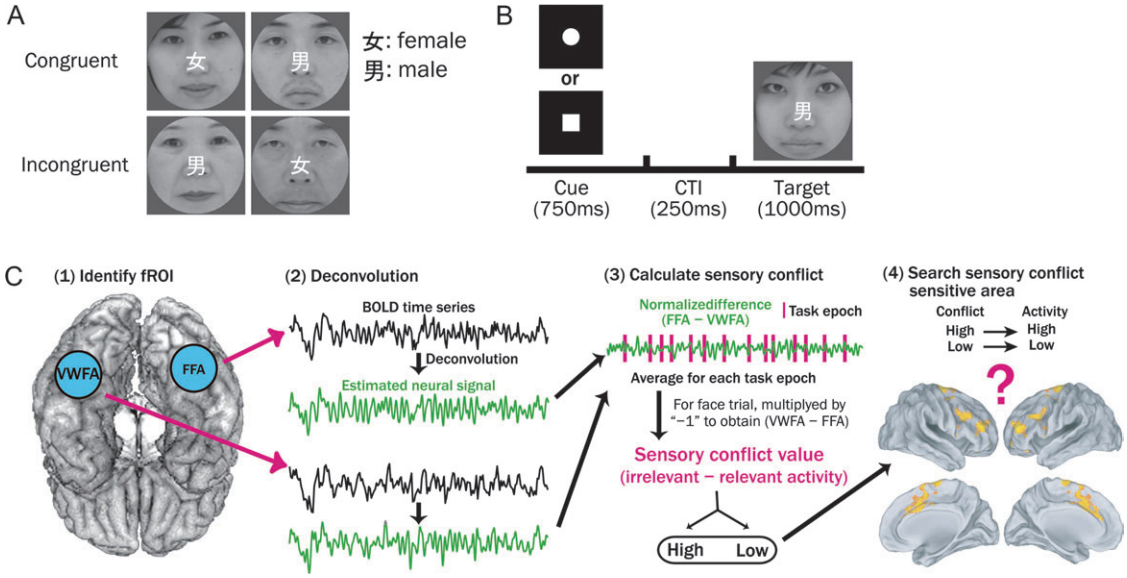

Figure 1. Behavioral task and single-trial analysis: (*A*) Example of stimuli. Upper panels represent stimuli for congruent trials, in which the gender of face image is consistent with the meaning of kanji letter. Lower panels represent stimuli for incongruent trials, in which the gender of face image is inconsistent with the meaning of kanji letter. (*B*) Timeline of the behavioral task. For each trial, subjects were presented with overlapping face and word stimuli (target) for 1000 ms and classified the face or word as male or female based on a task cue. Circle and square cues indicated face and word tasks, respectively. The stimulus onset asynchrony between the task cue and target was 1000 ms. (*C*) Scheme of single-trial analysis. After defining FFA and VWFA for each subject (*1*), we estimated the neural activity in the 2 regions by deconvolving the time series of the BOLD signals with HRF (*2*). We then normalized the estimated neural activation for each ROI and for each scanning session. For each trial, the difference in neural activation was calculated by subtracting the activity in the task-relevant area from that in the task-irrelevant area (*3*). The sensory conflict values thus calculated were used to categorize trials into high- or low-sensory conflict trials. Within the prefrontal regions that show significant activation during incongruent trials relative to the baseline ($P < 0.05$, corrected, shown in yellow on the surface of the MNI template brain), we looked for activation that is larger on high-sensory conflict trials than on low-sensory conflict trials (*4*).

angle of the target stimulus was about 6°. The task cue was either a filled circle or square, and based on it, the subjects judged whether the word or face image indicates male or female (Fig. 1*B*). On each trial, the task cue was given 1 s before the target stimulus and changed unpredictably across trials. The trials can be categorized into congruent or incongruent according to whether the face and word indicate the same or different sex. Thus, the task was designed in a 2-by-2 fashion, with factors of task (face and word task) and congruency (congruent and incongruent trial). In one experimental session, 38 trials for each of the 4 conditions were given in a pseudorandom order with an intertrial interval of 3, 5, or 7 s. To minimize confounding effects resulting from the previous trial types, the order of the trial type was counterbalanced within each session such that each trial type of a given task and congruency was preceded equally often by congruent and incongruent trials and also equally often by face and word task trials. Thus, task-switch and task-repetition trials occurred equally often. Two sessions were tested for each subject.

fMRI Data Acquisition and Preprocessing

Imaging was performed using a 1.5-T scanner (Sonata; Siemens, Germany). The functional images sensitive to blood oxygen level–dependent (BOLD) contrasts were acquired by T2*-weighted echo planar imaging (repetition time (TR): 2.1 s; echo time (TE): 40 ms; in-plane resolution of 3 mm in 64 × 64 matrix; 25 slices; slice thickness of 5 mm; and no interslice gap). For a localizer task (described below) and the Stroop task, 300 and 490 volumes of the whole-brain images were acquired, respectively. The Stroop task experiments were conducted for 2 sessions. We used SPM2 (http://www.fil.ion.ucl.ac.uk/spm) for image data preprocessing and analysis. For each scanning session, the first 5 volumes were discarded. The remaining volumes were realigned to the first image and normalized to the standard brain of the Montreal Neurological Institute (MNI). For the Stroop task sessions, the images within a volume were sinc interpolated over time to correct for phase advance during volume acquisition. The data were spatially smoothed with a Gaussian kernel of full-width half-maximum at 8 mm. High-resolution structural T1-weighted magnetization prepared rapid gradient echo sequence images (TR = 9.5 s, TE = 4 ms, time to inversion = 600 ms, voxel size 1 × 1 × 1.5 mm, and 108 axial slices) were also acquired for all subjects.

fMRI Data Analysis—Functional Localizer Task

In order to define the functional region of interest (ROI) for the FFA and VWFA, we first conducted a localizer experiment, in which subjects passively viewed either a series of 10 face images or a series of 10 kanji letters in a block of 10 s. Each of the face image or kanji letter was presented for 750 ms followed by a blank period of 250 ms. Each of the face and kanji block was followed by a 10-s interblock interval and repeated for 10 times. To identify functional ROI for the FFA and VWFA, statistical parametric maps of *t*-statistics were calculated for condition-specific effects within a general linear model. Each of the face and kanji block was modeled as a box-car regressor starting from the onset of the first stimulus in a block to the end of the last stimulus in that block. All epochs were convolved with a canonical hemodynamic response function (HRF). The data were high-pass filtered with a frequency cut-off at 100 s. For each volume, global scaling was applied. For each subject, the ROI for the FFA was defined as a spherical region with a radius of 4 mm centered at the peak voxel within the fusiform gyrus that showed significantly higher activation in the face block than in the kanji block ($P < 0.005$, uncorrected). This was identified within the voxels that showed higher activation in the face block relative to the interblock interval ($P < 0.01$, uncorrected). The ROI for the VWFA was defined as a spherical region with a radius of 4 mm centered at the peak voxel showing significantly higher activation in the kanji block than in the face block ($P < 0.005$, uncorrected). This was identified within the voxels that showed higher activation in the kanji block relative to the interblock interval ($P < 0.01$, uncorrected).

fMRI Data Analysis—Stroop Task

For the Stroop task sessions, statistical parametric maps of *t*-statistics were calculated for condition-specific effects within a general linear model. Each of the face-congruent, face-incongruent, kanji-congruent, and kanji-incongruent trial was modeled as a 2-s epoch with a box-car

regressor starting from the onset of task cue to the offset of the target stimulus. Error trials were modeled separately. All epochs were convolved with a canonical HRF. Images of parameter estimates for incongruent trials were created for each subject (first-level analysis) and were then entered into a second-level analysis using a one-sample *t*-test across the subjects.

Previous studies have shown that the PFC and ACC play a major role in proactive control and resolution of conflict. We are interested in the possibility that similar regions in the PFC and ACC are also involved in reactive control but in different manners. Thus, we made an anatomical mask of the PFC with WFU_PickAtlas Version 2.4 (Maldjian et al. 2003). We determined the anatomical location of the PFC based on Talairach Daemon implemented in WFU_PickAtlas (Lancaster et al. 2000). We included the regions labeled as superior, middle, inferior, and medial frontal gyrus; orbital gyrus; and anterior cingulate; and cingulate gyrus. The posterior border of the anatomical mask on the medial surface was at the level of the anterior commissure (*Y* coordinate = 0). Within this prefrontal mask, the activation map for incongruent trials relative to the intertrial interval was thresholded at $P < 0.05$ corrected for false discovery rate (Genovese et al. 2002). To visualize the activation map on the surface brain, we used CARET version 5 (http://brainmap.wustl.edu).

To examine areas in which activation was covaried with the level of sensory conflict, we first extracted BOLD signal time series from the ROI for the FFA and VWFA identified in the localizer task (Fig. 1*C*). We next obtained estimates of the neural activity from the BOLD time series by deconvolving the HRF using "spm_peb_ppi.m" function implemented in SPM2 for psychophysiological interaction and dynamic causal modeling analysis (Friston et al. 1997, 2003; Gitelman et al. 2003). This function uses Bayesian a priori assumption for the deconvolution and estimates 16 time points of neural signal in each volume acquisition. We normalized the estimated neural activity for each ROI and each session. For each trial epoch, we averaged the estimated neural activity (16 data points) and calculated the difference in the averaged neural activity between task-irrelevant areas (VWFA and FFA for face and word tasks, respectively) and task-relevant areas (FFA and VWFA for face and word tasks, respectively). For each of the congruent and incongruent trials, we sorted the trials based on the value calculated by subtracting the averaged activation during the 2-s task epoch in task-relevant from that in task-irrelevant visual areas. We then divided all trials into halves by the median of the differential activation. We called trials with larger values for task-irrelevant minus task-relevant visual areas as high-sensory conflict trials and trials with smaller values for task-irrelevant minus task-relevant visual areas as low-sensory conflict trials.

To search areas in which activation was covaried with the level of sensory conflict, we modeled all incongruent trials with correct response as one regressor with weighting of 1 and −1 for high- and low-sensory conflict trials, respectively. We also modeled all congruent trials in the same manner. Error trials were modeled separately without weighting of sensory conflict. Images of parameter estimates for the regressor on incongruent trials with weighting of two levels of sensory conflict were created for each subject and were then entered into a second-level analysis using one-sample *t*-test across the subjects. Within the prefrontal regions that showed significantly higher activation on incongruent trials relative to the baseline ($P < 0.05$, corrected), the results were thresholded at $P < 0.001$ uncorrected with spatial extent more than 5 voxels.

We then examined the psychophysiological interaction between the activation in areas identified in the above analysis and trial types with high- or low-sensory conflict (Friston et al. 1997, 2003). This is to identify areas that are functionally coupled with areas covaried with the level of sensory conflict but in different manners based on whether the sensory conflict was high or low. We extracted the BOLD time series from a spherical region with a radius of 4 mm centered at the peak coordinates of the DLPFC activation, which was identified by the analysis of the effect of sensory conflict on incongruent trials (MNI [*x y z*] = [−44 42 14]). We then obtained estimated neural activity by deconvolving the BOLD time series with the HRF. We calculated the product of this time course of estimated neural activity in the DLPFC and the vector of the psychological variable of interest with high- and low-sensory conflict trials weighted with 1 and −1, respectively. The psychophysiological interaction term thus calculated was convolved with canonical HRF. For each subject, a general linear model was computed, which includes, as regressors, the interaction term, the time series of BOLD signals in the DLPFC, and the psychological variable. Images of the parameter estimates for the interaction term on incongruent trials were created for each subject and were then entered into a second-level analysis using a one-sample *t*-test across the subjects. The results were masked with activation map of incongruent trials within the PFC ($P < 0.05$, corrected) and were thresholded at $P < 0.001$ uncorrected with spatial extent more than 5 voxels. The analysis has shown significant psychophysiological interaction between the DLPFC and ACC.

Finally, we examined the relationship between the behavioral response time and activation in the DLPFC and ACC. We extracted the deconvolved time series of the DLPFC and ACC activation from a spherical region with a radius of 4 mm centered at the peak voxel in the DLPFC ([*x y z*] = [−44 42 14]) and ACC ([*x y z*] = [12 18 48]). We then averaged the deconvolved activation for each trial epoch. For each of the high- and low-sensory conflict trials, we further classified the trials into 2 groups based on the scaled behavioral response time split by the median. We then calculated Pearson's correlation coefficient *r* for each of the fast and slow response trials and for each subject. After normalizing the correlation coefficient using Fisher transformation, we performed a one-sample *t*-test across subjects to examine whether the normalized coefficients were significantly larger than zero.

Results

Behavior

We found a significant main effect of congruency (incongruent vs. congruent) for both response time and accuracy (response time, $F(1, 15) = 16.36$, $P = 0.001$; accuracy, $F(1, 16) = 7.09$, $P = 0.019$) (Fig. 2). The response time was significantly larger, and accuracy was significantly lower on incongruent than on congruent trials. We also found a significant main effect of task, with better performance on the word task than on the face task (response time, $F(1, 15) = 25.65$, $P < 0.001$; accuracy, $F(1, 16) = 6.44$, $P = 0.024$). The interaction between congruency and task was also significant (response time, $F(1, 15) = 18.11$, $P = 0.001$; accuracy, $F(1, 16) = 5.57$, $P = 0.033$). However, for each of the face and word tasks, there was significant difference in the behavioral performance between incongruent and congruent trials, indicating the presence of cognitive conflict in both tasks (post hoc analysis, response time, face task $P < 0.001$; word task, $P = 0.04$; accuracy, face task $P = 0.002$; and word task, $P = 0.04$).

Neural Estimates of Sensory Conflict

In order to obtain the neural estimate of the sensory conflict, we first obtained, for each subject, the time series of BOLD signals from the FFA and VWFA, which were defined based on a separate functional localizer experiment. The mean

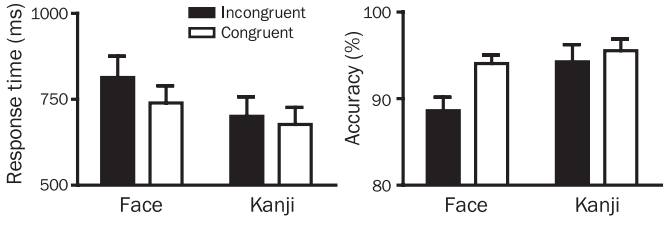

Figure 2. Behavioral results mean response time and correct rate are plotted for incongruent (black) and congruent (white) trials in the face and word tasks. Error bars indicate standard error across subjects.

coordinates of the identified ROI across subjects was (45, –52, –22) for the FFA and (–52, –62, –12) for the VWFA, which were consistent with previous studies (Kanwisher et al. 1997; Cohen et al. 2000; Grill-Spector and Malach 2004). The standard deviation of the coordinate across subjects was less than 8 mm for all axes of the coordinate, indicating consistency of the location of the FFA and VWFA.

We next examined activation in these ROIs during the Stroop task sessions. It has been shown that there is an increase in activation in visual association areas that process task-relevant information (Kastner and Ungerleider 2000; de Fockert et al. 2001; Egner and Hirsch 2005; Gazzaley et al. 2005a, 2005b, 2007; Morishima et al. 2009). We indeed found significantly higher activation in the FFA on face trials than on word trials ($t(14)$ = 3.58, P = 0.003), which suggests task-dependent modulation of activation in feature-specific sensory areas. In contrast, activation in the VWFA was not significantly higher on word trials than on face trials ($t(14)$ = 0.62, P = 0.54). The lack of task-dependent modulation of activation in the VWFA may be due to the lower demand of the word task: The performance of the subjects was significantly faster and more accurate in the word task than in the face task. Also, there was a significant interaction between task and congruency, with smaller congruency effect in the word task.

In the present study, we did not focus on the proactive control mechanism with which the processing in task-relevant sensory areas is facilitated in response to the task-instructing cue. Rather, we examined the mechanism with which the cognitive control system adjusts itself to the across-trial fluctuation in the level of activation in sensory areas upon arrival of sensory information. Our hypothesis was that the difference in activation between task-relevant and task-irrelevant areas triggers the reactive control mechanism so as to adjust the behavior according to the task requirement. We call this differential activation as the neural estimate of sensory conflict between task-relevant and task-irrelevant sensory information.

To obtain the neural estimates of sensory conflict, we first transformed the BOLD signals in the FFA and VWFA to neural activity by deconvolving the HRF from the BOLD time series. This procedure allowed us to estimate the neural activity in the FFA and VWFA for each trial. We calculated, on a single-trial basis, the difference in the estimate of neural activity between task-irrelevant and task-relevant visual areas by subtracting the activation in the FFA from that of VWFA for the face task and the activation in the VWFA from that of FFA for the word task. The mean sensory conflict value did not differ significantly between congruent and incongruent trials (incongruent: –0.0039, congruent: –0.0026, $t(14)$ = 0.039, P = 0.69).

Behavioral Relevance of Sensory Conflict

A larger amount of activation in areas that process task-irrelevant sensory information relative to that in areas that process task-relevant sensory information indicates a higher level of sensory conflict, which has to be resolved in order to regulate the behavior in favor of task-relevant information. Based on the idea, we classified all trials into high- or low-sensory conflict trials depending on whether the difference in activation in these visual areas was larger or smaller than the median of the differential activation for all trials.

It was predicted that a larger amount of sensory conflict is associated with an increase in reaction time on incongruent trials because of the need to resolve the conflict and adjust the response accordingly. In contrast, on congruent trials, we predicted that the amount of sensory conflict does not affect response time because both task-relevant and task-irrelevant sensory information lead to the same behavioral response and thus do not result in response competition. To test the idea, for each of incongruent and congruent trials, we categorized high-sensory conflict trials into 3 bins based on response time and compared sensory conflict values between the fastest and slowest bins. As predicted, we found that, on incongruent trials with high-sensory conflict, the sensory conflict value was significantly higher in the slowest bin than that in the fastest bin ($t(14)$ = 2.497, P = 0.025), whereas no significant difference was observed between fastest and slowest bins on congruent trials with high-sensory conflict ($t(14)$ = 0.056, P = 0.955) (Fig. 3). The results support the behavioral relevance of the sensory conflict values.

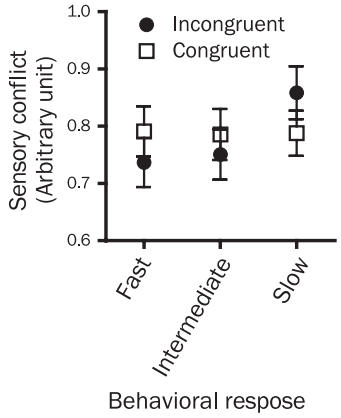

Figure 3. Relationship between sensory conflict and behavior Mean sensory conflict values are plotted for trials with fast, intermediate, and slow responses, for incongruent (black circle) and congruent (white square) trials with high-sensory conflict. Error bars indicate standard error across subjects.

We have also examined the correlation between sensory conflict value and response time (RT). For each subject, we calculated Pearson's correlation coefficient r between sensory conflict and RT, and the one-sample t-test was then performed on standardized r across 15 subjects. On incongruent trials with high-sensory conflict, the correlation was not significant but was close to the threshold (mean value: 0.058, $t(14)$ = 1.90, P = 0.07). On congruent trials with high-sensory conflict, the correlation was not significant (mean value: –0.008, $t(14)$ = –0.31, P = 0.75). Although we consider that the sensory conflict could contribute to the variability in RT on the incongruent trial with high-sensory conflict, the association between sensory conflict and RT was not strong. This may be because the association was obscured by the trial-by-trial fluctuation of the processing at a response selection stage.

We also predicted that the level of sensory conflict changes depending on whether the subjects had performed congruent or incongruent trials on the previous trial. It has been shown that performance of the subjects on incongruent trials is improved when the trial is preceded by an incongruent trial (Kerns et al. 2004; Egner and Hirsch 2005; Mansouri et al. 2009). In fact, the response time of our subjects was significantly shorter on incongruent trials preceded by an incongruent trial than on those preceded by a congruent trial ($t(14)$ = 2.94, P = 0.01). This behavioral effect is thought to be due to the carryover of control

signals engaged in the prior performance of incongruent trials. We considered that this conflict adaptation effect is also observed on the level of sensory conflict. Concurrent with the idea, we found that the estimate of sensory conflict on incongruent trials preceded by an incongruent trial was significantly less than zero ($t(14) = -2.469$, $p = 0.027$), indicating that activation in the task-relevant areas was higher than that in task-irrelevant areas. The results suggest that the sensory conflict was modulated by conflict adaptation.

Activation in the DLPFC Changes Depending on the Level of Sensory Conflict

The first aim of the present study was to find areas in which activation was modulated depending on the level of conflict between competing sensory representations. In other words, we looked for areas that responded to the online fluctuation in the inputs to the cognitive control system. These areas are considered to be recruited more on incongruent trials than on congruent trials. Therefore, we looked for these conflict-related areas within regions in which activation was higher on incongruent trials than on intertrial intervals. We found that the bilateral middle and inferior frontal gyrus, bilateral superior frontal sulcus, and the broad extent of medial PFC were active on incongruent trials ($P < 0.05$, corrected) (Fig. 1*C*).

We then looked for areas in which activation changed depending on the level of sensory conflict within the prefrontal regions that were active on incongruent trials (Fig. 1*C*, thresholded at $P < 0.05$ corrected). We found that activation in the left DLPFC (Brodmanns area 46) was significantly higher on trials with a high level of sensory conflict ($P < 0.001$, uncorrected, peak coordinate [*x y z*] = [–44 42 14], *z*-score = 3.28) (Fig. 4*A*). Moreover, the association was observed only on incongruent trials: The activation in this area was not covaried with the level of sensory conflict on congruent trials ($P = 0.42$) (Fig. 4*B*). We also searched brain areas in which activation covaried parametrically with the sensory conflict value for each trial. We again found that activation in the DLPFC was significantly covaried with the sensory conflict only on incongruent trials (peak coordinate: [–44 44 12], *z*-score: 3.11). The result supports tight association between sensory conflict value and activation in the DLPFC. Of note is that activation in the DLPFC was modulated by sensory conflict only when the conflict has to be resolved for the current behavioral goal.

We further examined the possibility that the association between activation in the DLPFC and the level of sensory conflict can be accounted for by the difference in performance between the face and word tasks. We tested the effect of task and sensory conflict level on activation in the DLPFC. Again, we found a significant main effect of sensory conflict level ($F(1,14) = 10.874$, $P = 0.005$). However, the main effect of the tasks ($F(1,14) = 2.361$, $P = 0.15$) and interaction between sensory conflict and task types were not significant ($F(1,14) = 1.17$, $P = 0.30$). Thus the association between activation in the DLPFC and the level of sensory conflict cannot be accounted for by the difference in performance between the face and word tasks.

We also examined whether a task-switch effect can account for the activation in the DLPFC. We created another general linear model in which task-switch and task-repetition trials were modeled as an additional regressor. We found that addition of the task-switch regressor did not affect the covariation of the DLPFC activation with the level of sensory conflict: The peak of the significant covariation was found at coordinate [–44 44 12] ($z = 3.34$). In this region, the parameter estimate for the task-switch regressor was not significantly different from zero ($P > 0.05$, uncorrected). Thus, the association between the DLPFC and sensory conflict cannot be accounted for by the task switch.

We also found that activation in the DLPFC was not significantly correlated with across-trial fluctuation in the response time ($P > 0.05$, uncorrected), suggesting that the activation cannot be accounted for by the fluctuation in behavioral response time. However, when we analyzed only the high-sensory conflict trials, the DLPFC activation was significantly correlated with response time ($t(14) = 3.93$, $P = 0.0015$) (Fig. 4*C*), with a higher amount of activation covaried with slower response. The correlation was not significant in low-sensory conflict trials ($t(14) = -0.60$, $P = 0.55$). The correlation in high-sensory conflict trials was significantly higher than the correlation in low-sensory conflict trials ($t(14) = 4.096$, $P = 0.0011$). The results suggest that the DLPFC plays a role in detection of sensory conflict in a goal-dependent manner.

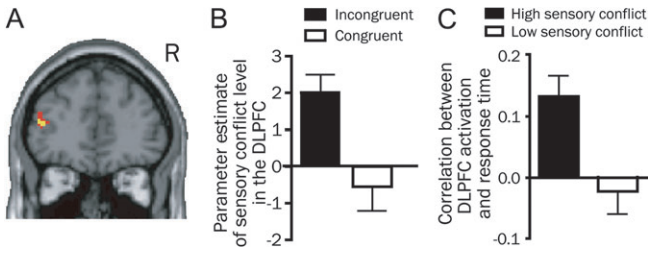

Figure 4. Activation associated with sensory conflict in the DLPFC: (*A*) Activation in the DLPFC (coordinate: −44, 42, 14) associated with sensory conflict level. For visualization purpose, red and yellow voxels correspond to $P < 0.005$ and $P < 0.001$ uncorrected, respectively. (*B*) Parameter estimates of the sensory conflict-related regressor in the DLPFC (coordinate: −44, 42, 14). This reflects the sensitivity to the level of sensory conflict. Beta estimates on incongruent trials (black) are significant larger compared with those on congruent trials ($t(14) = 3.00$, $P = 0.009$). Beta estimates on congruent trials (white) are not significantly different from zero ($P = 0.42$). Error bars indicate standard error across subjects. (*C*) Correlation between DLPFC activation and response time. Across-subject means of the normalized correlation coefficients are plotted separately for high-sensory conflict and low-sensory conflict trials. Error bars indicate standard error across subjects.

The Coupling between the DLPFC and ACC Is Associated with Behavior during High-Sensory Conflict

The second aim of the present study is to clarify the mechanism with which the inputs of the conflict information to the cognitive control system are implemented for the adjustment of behavior. In other words, we examined the neural substrate for a reactive mechanism of conflict resolution. For this purpose, we looked for areas in which activation is correlated with activation in the DLPFC on incongruent trials with high-sensory conflict (Friston et al. 1997; Gitelman et al. 2003). Among the prefrontal regions that were active on incongruent trials ($P < 0.05$, corrected), we found that activation in the ACC was significantly correlated with activation in the DLPFC, suggesting a functional link between the two regions ($P < 0.001$, uncorrected, peak coordinate [*x y z*] = [12 18 48], *z*-score = 3.54) (Fig. 5*A*).

We found evidence supporting the idea that the network between the DLFPC and ACC is involved in the regulation of behavior. For each of the high- or low-sensory conflict trials, we divided trials into halves based on the median of the scaled response time. We found significant correlation between activation in the DLPFC and ACC on high-sensory conflict trials

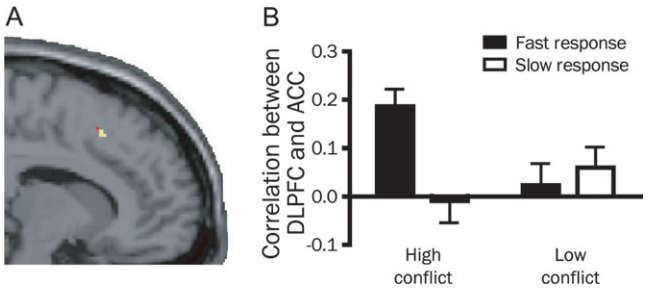

Figure 5. The ACC coupled with the DLPFC during incongruent trials with high-sensory conflict: (*A*) Psychophysiological interaction between the DLPFC activation and sensory conflict level. The ACC (coordinate: 12, 18, 48) is significantly coupled with the DLPFC in high-sensory conflict trials. For visualization purpose, red and yellow voxels correspond to $P < 0.005$ and $P < 0.001$ uncorrected, respectively. (*B*) Behavioral relevance of coupling between the DLPFC and ACC. Normalized correlation coefficient between activation in the DLPFC and ACC is plotted for each of the high- and low-sensory conflict trials with fast (black) and slow (white) responses. There is a significant correlation in activation between the DLPFC and ACC on faster response trials with high-sensory conflict ($P < 0.001$), whereas this is not significant on slower response trials with high-sensory conflict. Error bars indicate standard error across subjects.

with a faster response ($t(14) = 5.22$, $P < 0.001$), but the correlation was not significant in the high-sensory conflict trials with a slower response ($t(14) = 0.51$, $P = 0.61$) (Fig. 5*B*). We also found that the correlation on high-sensory conflict trials with a faster response was significantly tighter than a slower response ($t(14) = 3.556$, $P = 0.003$). The correlation was not significant on low-sensory conflict trials, either, regardless of response speed (fast response $t(14) = -0.19$, $P = 0.85$; slow response $t(14) = 1.44$, $P = 0.17$). In sum, the tight coupling between the DLPFC and ACC was observed when there was a high level of sensory conflict and when the subjects were able to respond quickly, suggesting that the interaction between the two areas is associated with resolution of sensory conflict. The amount of activation in the ACC did not differ significantly between fast and slow response trials with high-sensory conflict ($t(14) = -1.14$, $P = 0.27$), suggesting that the tight coupling between the DLPFC and ACC rather than activation in a single ACC region is necessary for faster response.

Discussion

The aim of the present study is to elucidate how the cognitive control process is adjusted to the sensory conflict for online regulation of behavior. We sorted trials based on the amount of sensory conflict, defined by the difference in brain activation between task-relevant and task-irrelevant visual association areas. The analysis enables us to isolate sensory conflict from response conflict. We found that activation in the DLPFC was covaried with the level of sensory conflict only when the conflict needs to be resolved for current behavioral goal. We also found that the tight coupling between the DLPFC and ACC was associated with faster response on high-sensory conflict trials. The results suggest that a reactive cognitive control mechanism is subserved by a chain of interacting networks, whereby conflicts between sensory information are detected and are used to regulate behavior.

Conflict-Driven Networks Identified with Single-Trial Analysis

Single-trial analysis is essential to elucidate fluctuations in cognitive functions (Fox and Raichle 2007; Fox et al. 2007; Eichele et al. 2008). Fox et al. (2007) have shown a tight association between the fluctuation of BOLD signal in sensori-motor cortices and variability in button press force. Eichele et al. (2008) have shown that an increase in activation in the default mode network predicts poor behavioral performance on a trial 30 s later. These studies have examined whether the fluctuation of brain activation can explain behavioral fluctuation. In the present study, we have identified an interacting brain network that is driven by across-trial fluctuations in activation in sensory areas. Neural mechanisms of cognitive control have been examined by comparing brain activation between congruent and incongruent trials, which are categorically defined based on the congruency of the stimuli presented. However, activation in sensory areas that process the stimuli fluctuates across trials even within the same experimental condition. In the present study, we have identified brain areas in which activation was covaried with the trial-by-trial fluctuation in the neural estimates of conflict at a sensory processing stage.

We calculated, on a single-trial basis, the difference in brain activation between task-relevant and task-irrelevant visual association areas, which we considered as reflecting the level of conflict at a sensory processing stage. This neural estimate of sensory conflict was shown to be associated with behavior: A higher sensory conflict value was associated with slower behavioral response on incongruent trials, and conflict adaptation effect was observed on both the response time and sensory conflict values. We further found that the sensory conflict did not affect the speed of behavioral response on congruent trials. We interpret the results based on a model proposed by Cohen et al. (1990). In this model, noise components are implemented as a source of behavioral variability at both sensory processing and response selection stages. It is considered that, on incongruent trials, fluctuation in the processing at a sensory stage contributes to the across-trial variability in behavioral response time, whereas the fluctuation does not influence the response time on congruent trials because both task-relevant and task-irrelevant sensory information lead to the same behavioral response. However, the correlation between the sensory conflict and response time was not strong even on incongruent trials because there exists an additional noise component at a response selection stage. In fact, we have identified separate neural mechanisms that are involved in detection of sensory conflict and adjustment of behavioral response.

Roles of the DLPFC for Conflict Detection

Our results suggest that the DLPFC detects the sensory conflict in a manner dependent on the behavioral goal. Activation in the DLPFC was covaried with the magnitude of sensory conflict, which was defined by the difference in activation between task-irrelevant minus task-relevant visual areas on a given trial. This suggests that the DLPFC responds to the conflict information from sensory areas that process task-relevant and task-irrelevant information in the sensory stimuli. The association between the DLPFC activation and estimate of sensory conflict was observed only in incongruent trials, which suggests that the DLPFC responds to the sensory conflict only when the conflict needs to be resolved for response selection.

Previous studies have shown an increase of activation in the ACC in tasks that involves detection and resolution of conflict. However, the ACC is not connected with visual association cortices but is connected with the lateral prefrontal and motor

cortices (Picard and Strick 1996; Barbas 2000). Thus, it is less likely that the ACC receives direct inputs from sensory areas and detects sensory conflict. In contrast, the DLPFC is tightly connected with the visual association cortices (Barbas 2000). Furthermore, single-unit studies have also shown that neurons in the DLPFC represent a combination of sensory information and behavioral goal, whereas neurons in the medial PFC, including the ACC, represent behavioral response and reward likelihood, not sensory information (Lauwereyns et al. 2001; Shidara and Richmond 2002; Matsumoto et al. 2003, 2007). We consider that the DLPFC, rather than the ACC, is situated in a position to detect sensory conflict information.

In fact, previous imaging and brain lesion studies have shown that the DLPFC plays a critical role in situations with sensory conflict. Gehring et al. have shown that, in patients with DLPFC lesion, the amplitude of error-related negativity on the vertex is comparable with the amplitude of event-related potential on correct trials, whereas in age-matched control subjects, the event-related potential on the vertex is significantly larger on error trials than that on correct trials (Gehring and Knight 2000). Braver et al. (2003) have shown that the DLPFC but not the ACC is active in response to bottom-up driven information. Milham et al. (2003) have shown that the ACC is primarily involved in response-related conflict . Liston et al. (2006) have shown that the DLPFC is more active when subjects switch between the feature domains to be attended. Tsushima et al. (2006) have shown an increase in the DLPFC activation when identification of rapidly presented letters is perturbed by ambiguous motion background. Those studies indicate that the DLPFC responds to conflicting sensory information, but it is not clear whether the DLPFC activation is related to the detection or resolution of conflict. In the present study, by introducing single-trial analysis, we have shown that the DLPFC may play a role in detecting sensory conflict in a goal-dependent manner.

The DLPFC may not only play a role in detection of sensory conflict but also in resolution of the conflict. A higher amount of activation in the DLPFC on trials with a high level of sensory conflict may reflect processes associated with biasing the competition in favor of task-relevant sensory information. However, higher activation in the DLPFC was associated with an increase in the response time, suggesting that DLPFC activation in response to sensory conflict is not sufficient to resolve sensory conflict.

Reactive Mechanism for Conflict Resolution

Once the sensory conflict is detected in the DLPFC, the information needs to be transferred to areas more related to response selection so as to adjust behavior in a task-contingent manner. We found that activation in the ACC is positively correlated with activation in the DLPFC when there was a high level of sensory conflict, which may suggest that the ACC receives sensory conflict information from the DLPFC. We have also shown that tight coupling between the DLPFC and ACC is associated with faster behavioral response when the level of sensory conflict is high. We also found that the amount of activation in the ACC was not associated with response time. Based on these, we suggest that the interaction between the DLPFC and ACC is driven by an increase in the bottom-up inputs related to sensory conflict, and this contributes to online resolution of conflict. In contrast to the proactive mechanism for conflict resolution, we call this sensory-driven mechanism a reactive mechanism for conflict resolution (Braver et al. 2003; Bunge 2004).

Previous studies have shown that the ACC plays an essential role in adjustment of executive control mechanism of the DLPFC (Botvinick et al. 2001; Kerns et al. 2004; Brown and Braver 2005; Egner and Hirsch 2005; di Pellegrino et al. 2007; Mansouri et al. 2007; Mansouri et al. 2009). The activation of the ACC on a given trial predicts the activation of the DLPFC on the next trial (Kerns et al. 2004). Patients with ACC lesion do not exhibit behavioral adjustments in cognitive control following the occurrence of response conflict (di Pellegrino et al. 2007). According to the conflict monitoring account, conflict adaptation effect is achieved as a passive consequence of dealing with conflict information on a previous trial (Botvinick et al. 2001). Thus, the information may flow from the ACC to DLPFC for regulation of behavior across trials.

In contrast, the present study has examined a reactive control mechanism involved in resolution of sensory conflict that starts to operate upon arrival of sensory information. In this reactive control, we propose that the information may flow from the DLPFC to ACC. The DLPFC detects sensory conflict that has to be resolved for the current behavioral goal. The detected conflict is then resolved at the response level through tight coupling between the DLPFC and ACC (Fig. 6). The idea is consistent with cascade-of-control model proposed by Banich et al. (2009). They propose that the DLPFC biases task-relevant processes and representations, and the ACC then evaluates and selects behavioral response. Previous studies have shown that the ACC as well as the presupplementary motor area play a role in regulating behavior in the presence of conflicts between two opposing responses (Carter et al. 1998; Botvinick et al. 1999; MacDonald et al. 2000; Barch et al. 2001; Swick and Jovanovic 2002; Kerns et al. 2004; Brown and Braver 2005; Isoda and Hikosaka 2007; Taylor et al. 2007). The present study has advanced the idea by demonstrating that efficient interaction between the ACC and DLPFC is necessary to resolve conflicts. The tight coupling may reflect efficient transfer of conflict information between the two areas. The conflict is then resolved at a response selection stage rather than a sensory processing stage.

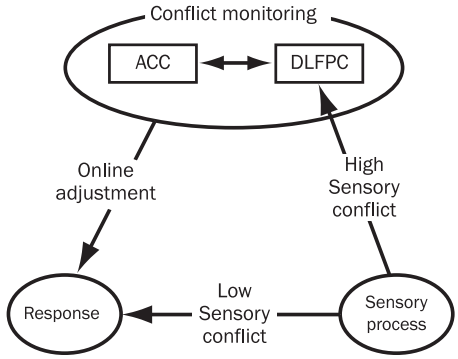

Figure 6. Reactive control model for online conflict resolution: When the level of conflict at a sensory processing stage is high, the conflict is detected by a detector of the conflict monitoring system, the DLPFC. The DLPFC then communicates with an effector of the conflict monitoring system, the ACC and transfers the conflict information. The tight functional link between the DLPFC and ACC enables effective adjustment of behavior and thus results in faster behavioral response. By contrast, when the level of conflict at a sensory processing stage is low, the sensory information is directly transferred from a sensory processing unit to a response unit.

In conclusion, we have identified neural substrates for an online adaptive control mechanism, whereby conflicts between task-relevant and task-irrelevant sensory information are detected and used to adjust the behavior. The DLPFC detects sensory conflict that has to be resolved for goal-directed behavior, but activation in the DLPFC itself is not sufficient to resolve the conflict. Instead, tight coupling between the DLPFC and ACC resolves the sensory conflict, but activation in the ACC per se is not sufficient to resolve the conflict. Adaptive control of behavior is achieved by interacting neural networks in the PFC.

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Notes

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References

Banich MT, Mackiewicz KL, Depue BE, Whitmer AJ, Miller GA, Heller W. 2009. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. Neurosci Biobehav Rev. 33:613–630.

Barbas H. 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull. 52:319–330.

Barch DM, Braver TS, Akbudak E, Conturo T, Ollinger J, Snyder A. 2001. Anterior cingulate cortex and response conflict: effects of response modality and processing domain. Cereb Cortex. 11:837–848.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature. 402:179–181.

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. 2001. Conflict monitoring and cognitive control. Psychol Rev. 108:624–652.

Braver TS, Reynolds JR, Donaldson DI. 2003. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron. 39:713–726.

Brown JW, Braver TS. 2005. Learned predictions of error likelihood in the anterior cingulate cortex. Science. 307:1118–1121.

Bunge SA. 2004. How we use rules to select actions: a review of evidence from cognitive neuroscience. Cogn Affect Behav Neurosci. 4:564–579.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science. 280:747–749.

Cohen JD, Dunbar K, McClelland JL. 1990. On the control of automatic processes: a parallel distributed processing account of the Stroop effect. Psychol Rev. 97:332–361.

Cohen L, Dehaene S, Naccache L, Lehericy S, Dehaene-Lambertz G, Henaff MA, Michel F. 2000. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain. 123(Pt 2):291–307.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 3:201–215.

de Fockert JW, Rees G, Frith CD, Lavie N. 2001. The role of working memory in visual selective attention. Science. 291:1803–1806.

Desimone R, Duncan J. 1995. Neural mechanisms of selective visual attention. Annu Rev Neurosci. 18:193–222.

di Pellegrino G, Ciaramelli E, Ladavas E. 2007. The regulation of cognitive control following rostral anterior cingulate cortex lesion in humans. J Cogn Neurosci. 19:275–286.

Egner T, Hirsch J. 2005. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat Neurosci. 8:1784–1790.

Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, von Cramon DY, Ullsperger M. 2008. Prediction of human errors by maladaptive changes in event-related brain networks. Proc Natl Acad Sci U S A. 105:6173–6178.

Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 8:700–711.

Fox MD, Snyder AZ, Vincent JL, Raichle ME. 2007. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron. 56:171–184.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 6:218–229.

Friston KJ, Harrison L, Penny W. 2003. Dynamic causal modelling. Neuroimage. 19:1273–1302.

Gazzaley A, Cooney JW, McEvoy K, Knight RT, D'Esposito M. 2005a. Top-down enhancement and suppression of the magnitude and speed of neural activity. J Cogn Neurosci. 17:507–517.

Gazzaley A, Cooney JW, Rissman J, D'Esposito M. 2005b. Top-down suppression deficit underlies working memory impairment in normal aging. Nat Neurosci. 8:1298–1300.

Gazzaley A, Rissman J, Cooney J, Rutman A, Seibert T, Clapp W, D'Esposito M. 2007. Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. Cereb Cortex. 17(Suppl. 1):1125–135.

Gehring WJ, Knight RT. 2000. Prefrontal-cingulate interactions in action monitoring. Nat Neurosci. 3:516–520.

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 15:870–878.

Gitelman DR, Penny WD, Ashburner J, Friston KJ. 2003. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. Neuroimage. 19:200–207.

Gratton G, Coles MG, Donchin E. 1992. Optimizing the use of information: strategic control of activation of responses. J Exp Psychol Gen. 121:480–506.

Grill-Spector K, Malach R. 2004. The human visual cortex. Annu Rev Neurosci. 27:649–677.

Isoda M, Hikosaka O. 2007. Switching from automatic to controlled action by monkey medial frontal cortex. Nat Neurosci. 10:240–248.

Kanwisher N, McDermott J, Chun MM. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci. 17:4302–4311.

Kastner S, Ungerleider LG. 2000. Mechanisms of visual attention in the human cortex. Annu Rev Neurosci. 23:315–341.

Kerns JG, Cohen JD, MacDonald AW, 3rd, Cho RY, Stenger VA, Carter CS. 2004. Anterior cingulate conflict monitoring and adjustments in control. Science. 303:1023–1026.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. 2000. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp. 10:120–131.

Lauwereyns J, Sakagami M, Tsutsui K, Kobayashi S, Koizumi M, Hikosaka O. 2001. Responses to task-irrelevant visual features by primate prefrontal neurons. J Neurophysiol. 86:2001–2010.

Liston C, Matalon S, Hare TA, Davidson MC, Casey BJ. 2006. Anterior cingulate and posterior parietal cortices are sensitive to dissociable forms of conflict in a task-switching paradigm. Neuron. 50:643–653.

MacDonald AW, 3rd, Cohen JD, Stenger VA, Carter CS. 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science. 288:1835–1838.

MacLeod CM. 1991. Half a century of research on the Stroop effect: an integrative review. Psychol Bull. 109:163–203.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 19:1233–1239.

Mansouri FA, Buckley MJ, Tanaka K. 2007. Mnemonic function of the dorsolateral prefrontal cortex in conflict-induced behavioral adjustment. Science. 318:987–990.

Mansouri FA, Tanaka K, Buckley MJ. 2009. Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. Nat Rev Neurosci. 10:141–152.
Matsumoto K, Suzuki W, Tanaka K. 2003. Neuronal correlates of goal-based motor selection in the prefrontal cortex. Science. 301:229–232.
Matsumoto M, Matsumoto K, Abe H, Tanaka K. 2007. Medial prefrontal cell activity signaling prediction errors of action values. Nat Neurosci. 10:647–656.
Milham MP, Banich MT, Claus ED, Cohen NJ. 2003. Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control. Neuroimage. 18:483–493.
Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 24:167–202.
Morishima Y, Akaishi R, Yamada Y, Okuda J, Toma K, Sakai K. 2009. Task-specific signal transmission from prefrontal cortex in visual selective attention. Nat Neurosci. 12:85–91.
Picard N, Strick PL. 1996. Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex. 6:342–353.
Shidara M, Richmond BJ. 2002. Anterior cingulate: single neuronal signals related to degree of reward expectancy. Science. 296: 1709–1711.
Swick D, Jovanovic J. 2002. Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. Neuropsychologia. 40:1240–1253.
Taylor PC, Nobre AC, Rushworth MF. 2007. Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation electroencephalography study. J Neurosci. 27: 11343–11353.
Tsushima Y, Sasaki Y, Watanabe T. 2006. Greater disruption due to failure of inhibitory control on an ambiguous distractor. Science. 314:1786–1788.