

The Functional Integration of the Anterior Cingulate Cortex during Conflict Processing

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Although functional activation of the anterior cingulate cortex (ACC) related to conflict processing has been studied extensively, the functional integration of the subdivisions of the ACC and other brain regions during conditions of conflict is still unclear. In this study, participants performed a task designed to elicit conflict processing by using flanker interference on target response while they were scanned using event-related functional magnetic resonance imaging. The physiological response of several brain regions in terms of an interaction between conflict processing and activity of the anterior rostral cingulate zone (RCZa) of the ACC, and the effective connectivity between this zone and other regions were examined using psychophysiological interaction analysis and dynamic causal modeling, respectively. There was significant integration of the RCZa with the caudal cingulate zone (CCZ) of the ACC and other brain regions such as the lateral prefrontal, primary, and supplementary motor areas above and beyond the main effect of conflict and baseline connectivity. The intrinsic connectivity from the RCZa to the CCZ was modulated by the context of conflict. These findings suggest that conflict processing is associated with the effective contribution of the RCZa to the neuronal activity of CCZ, as well as other cortical regions.

Keywords: anterior cingulate cortex, conflict processing, dynamic causal modeling, connectivity, psychophysiological interaction

Introduction

The anterior cingulate cortex (ACC) is heterogeneous in cytoarchitecture, anatomical connectivity, and in the functions it subserves (Paus 2001). Cytoarchitectonic features have been used to parcel the ACC into various subdivisions, each characterized by specific neuronal laminar distribution patterns (Vogt et al. 1992, 1995, 2005). Human studies have demonstrated the functional heterogeneity of the ACC with regard to cognitive and emotional processing. Whereas activation of the caudal region of the ACC correlates with cognitive functions such as attention (Mesulam 1981; Posner and Petersen 1990), the rostral and subcallosal portions of the ACC appear to be related to the regulation of emotional processing (Devinsky et al. 1995; Bush et al. 2000; Etkin et al. 2006). Based on recording of single-unit activity in the nonhuman primate cingulate motor area, it has been suggested that rostral cingulate motor area neurons are involved in such cognitive and motor functions as attention for action and response selection, whereas ventral cingulate motor area and dorsal cingulate motor area neurons are involved in motor preparation and execution (Isomura et al. 2003). These areas are comparable with the human anterior rostral cingulate zone (RCZa), posterior rostral cingulate zone (RCZp), and caudal cingulate zone (CCZ) (Picard and Strick 2001). Based on functional neuroimaging of humans, it has been

proposed that conflict processing, response selection, and movement execution are associated with the RCZa, RCZp, and CCZ, respectively (Picard and Strick 2001).

The subdivisions of the ACC exhibit distinct connections with a number of cortical areas. For example, Brodmann's areas 24 and 32 of the ACC are interconnected with dorsolateral frontal areas, and subgenual area 25 is interconnected with posterior orbitofrontal areas (Barbas and Pandya 1989; Morecraft et al. 1993; Drevets et al. 1997). Because of this, the ACC serves as a node in various networks subserving a wide range of functions that includes executive control of attention (Posner and Petersen 1990) and motor-related functions such as response selection, preparation, and execution (Frith et al. 1991; Paus et al. 1993). However, the traditional approach based on correlation for establishing precise structure-function relationships for the brain activity associated with certain cognitive processes is not sufficient to provide an understanding of the mechanism of the dynamic system of the brain (Stephan 2004). Instead, our understanding of these functions is likely to reflect emergent properties of the interactions of distinct structures. For example, a better understanding of conflict processing might arise from study of the interactions between the ACC and a structure such as the lateral prefrontal cortex, which has also been implicated in conflict processing (MacDonald et al. 2000; Botvinick et al. 2001; Fan, Flombaum, et al. 2003), rather than both as independently related to task demands. It is, therefore, important to verify the involvement of structures in such networks by determining both whether or not these structures exert influence over one another and the effect that changing task demands have on such influences in order to establish structure-function relationships.

Functional connectivity is defined as the temporal correlation between remote neurophysiological events, whereas effective connectivity is defined as the influence one neural system exerts over another (Friston 1995; Buchel and Friston 1997; Buchel 2004). A meta-analysis of coactivation of frontal lobe regions with the ACC in a large number of human imaging studies has shown that ACC activation is frequently linked with activation in the precentral gyrus, the superior, middle, and inferior frontal gyri, and the orbitomedial frontal gyrus, whereas the activation of the precentral gyrus and the supplementary motor area (SMA) is linked more with caudal than rostral ACC activation (Koski and Paus 2000). The functional connectivity between the ACC and prefrontal and other areas is also supported by recent findings in a study of ACC resting-state functional connectivity (Margulies et al. forthcoming). Because the functional connectivity between the caudal ACC and the primary and SMAs is not influenced by manual response or output rate, it has been suggested that the coactivation reflects

the underlying effective connectivity between caudal ACC and the primary and SMAs, rather than simply the concomitant occurrence of movement (Koski and Paus 2000).

Much work has been dedicated to the study of the role of the ACC in conflict processing and various studies using various paradigms have implicated mainly dorsal, although some ventral, regions of the ACC in this process (Bush et al. 2000). In spite of this, the effective connectivity of the ACC and other structures commonly found to be activated during conflict processing in humans is not well understood. Therefore, it is important to study context-dependent changes in coupling between these regions in order to reveal the connective structure (i.e., the causal interactions among separate areas) of this system for conflict processing (Posner et al. 2006). Psychophysiological interaction (PPI) analysis (Friston et al. 1997) and dynamic causal modeling (DCM) (Friston et al. 2003; Penny et al. 2004) offer ways to access functional interactions and to model the neural dynamics in a system beyond searching for structure–function correlations using standard convolution models in which all brain areas are assumed disconnected from each other. These methods also provide a distinct advantage over methods employed to study functional connectivity in the context of investigating structure–function relationships.

Task-related increases in the effective connectivity of the ACC have been identified using time-series data of functional magnetic resonance imaging (fMRI). A recent combined fMRI and event-related potential study of the impact of ACC modulation on attentional response showed modality-specific effective connectivity with increased ACC influence on the Heschl and superior temporal gyri for the auditory oddball task and on the striate cortex for the visual oddball task (Crottaz-Herbette and Menon 2006). This suggests that the ACC exerts top-down attentional control by enhancing the sensory signals for target stimuli to facilitate further processing and that such control is exerted over multiple sensory modalities. Further support for a role of rostral ACC in top-down control comes from a study demonstrating inhibition of amygdala activity during an emotional conflict task (Etkin et al. 2006). These extend the finding of increased task-related functional connectivity between the caudal ACC and the primary and SMAs and supports the hypothesis that the ACC directs attention by modulating activity in diverse cortical regions (Posner and Raichle 1994).

In this study we examined the effective connectivity of the ACC during conflict processing. Participants performed the attention network test (ANT), which incorporates a flanker interference component to measure the conflict effect, while they were scanned using fMRI. The functional influence that the RCZa of the ACC exerts over other brain regions was modeled using PPI analysis after the influence of the task-related main effect of conflict and the baseline activity of the RCZa were partialled out. The results of the PPI analysis and previous studies in human and nonhuman primates informed a hypothesis of the connectivity structure of the executive control network of attention, which was then tested using DCM. We hypothesized that the RCZa, which is involved in conflict processing, would integrate with posterior subdivisions of the ACC and other regions for response selection and execution. Specifically, the intrinsic connection between RCZa and other regions would be enhanced during conditions of conflict. Finally, we expected to find dissociation between the structures identified by the PPI, the main effect of conflict, and the baseline connectivity of the ACC.

Materials and Methods

Participants

Sixteen right-handed healthy adults (mean age = 27.2 years, SD = 5.7 years, range: 18–36 years; 8 women) participated in this study. A signed informed consent approved by the New York Presbyterian Hospital/Weill Medical College of Cornell University was obtained from each participant prior to the experiment.

Procedure

The ANT was used as the cognitive task for this study and fMRI was carried out using a 3-T General Electric Signa scanner. The ANT and the anatomical and fMRI data acquisition procedure have been described in detail previously (Fan et al. 2005). Figure 1 shows the flanker component of the ANT for eliciting conflict. The center arrow was the target. There were 2 target conditions: targets with congruent or incongruent flankers. The participants' task was to indicate the direction of the target, using the left index finger for left pointing targets and the right index finger for right pointing targets. Conflict processing was assessed by comparing responses to targets with incongruent flankers to responses to targets with congruent flankers. In addition to the flanker conflict component, the full ANT also included 3 cue conditions (no cue, center cue, and spatial cue). These cue conditions were implemented to assess the alerting and orienting components of attention reported in a previously publication (Fan et al. 2005). All analyses reported in this paper were performed with target-locked regressors collapsed across cue conditions.

Standard Convolution Model for fMRI Analysis

Image preprocessing was performed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK) as previously reported (Fan, Fossella, et al. 2003; Fan et al. 2005). For each subject, the cue-related conditions (no cue, center cue, and spatial cue) and 2 target-related conditions (target with congruent flankers or incongruent flankers) were first modeled as previously described (Fan et al. 2005) using conventional statistical parametric mapping (SPM2). Low frequency drifting was filtered with a cut-off period of 128 s and serial correlations were corrected using a first-order autoregressive model implemented in SPM2. The conflict effect was defined as the contrast of incongruent versus congruent conditions.

The coordinates of the seed ACC volume of interest (VOI) were determined from the coordinates ($x = 6$, $y = 36$, $z = 26$), which was located at RCZa, for the conflict effect in our previous study of the same subject group (Fan et al. 2005). Specifically, the seed ACC VOI was defined as a 6-mm radius sphere (e.g., Brazdil et al. 2007) at the local peak nearest to the relevant coordinate in the SPM for the target response contrast, which included targets with congruent and incongruent flankers, individually for each subject. The mean coordinates of the center of the VOI was $x = 5.3$ mm, $y = 32.1$ mm, and $z = 26.9$ mm with SD of 1.6, 5.7, 3.9 mm, respectively. The time series of the first

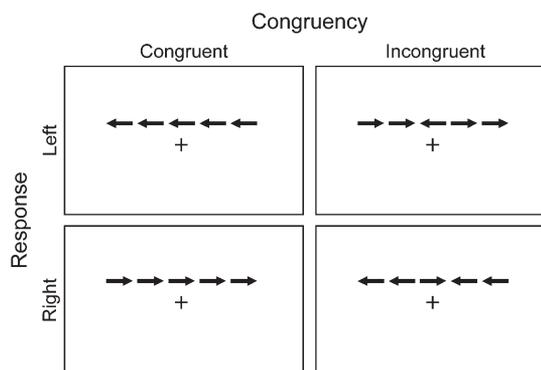


Figure 1. Illustration of the flanker task component for eliciting conflict in the ANT. There are 2 target conditions: targets with congruent or incongruent flankers, and 2 possible responses: left or right. The participants' task is to indicate the direction of the target, which is the center arrow. The center cross is the fixation point.

eigenvariate of the ACC VOI blood oxygen level-dependent (BOLD) signal, adjusted for effects of interest, was calculated from the time-series of voxels passing significance in the conflict contrast within this region. The mean volume of the VOI was 520 mm³, with a standard deviation of 233 mm³.

PPI Analysis

PPI, defined as the change in contribution of one brain area to another with the experimental or psychological context (Friston et al. 1997), was modeled using the PPI analysis in SPM2 (Friston et al. 1997; Gitelman et al. 2003). PPI computes whole-brain connectivity between the time series of the seed VOI and the time series of all other voxels. The bilinear term in PPI represents the interaction between physiological activity and a psychological context input, which modulates the connectivity between the seed VOI and the other brain regions, and has a directional character (Stephan 2004). The PPI analysis was an important first step in exploring the functional interactions of the ACC VOI across the whole brain during conflict processing.

The time-series data of the first eigenvariate of the seed VOI were temporally filtered and mean corrected as in conventional SPM analysis. Bayesian estimation was used to deconvolve the time series of the BOLD signal to generate the time series of the neuronal signal for the VOI. The time series of the neuronal signal for responses to the targets with incongruent and congruent flankers was created, resulting in one vector (the PPI regressor) representing the interaction between the psychological and physiological factors (the PPI variable), a second vector (the P regressor) representing the incongruent minus congruent contrast for the main effect of conflict (the psychological variable), and a third vector (the Y regressor) representing the VOI time course (the physiological variable). These regressors were forward-convolved with the canonical hemodynamic response function (HRF), and then entered into the regression model along with other vectors for cue events as well as effects of no interest, including the 6 motion correction parameters and sessions.

Model estimation was performed and the resulting SPM showed areas with significant differential connectivity to the VOI because of the context manipulations (i.e., incongruent vs. congruent flankers). PPI

analysis was carried out for each subject and the resulting images of contrast estimates were entered into a random effect group analysis. The significance level for each voxel was set at 0.01, with a cluster size larger than 80 resampled voxels with each voxel sized as 2 × 2 × 2 mm³, as decided by a Monte Carlo simulation to correct for multiple voxel comparisons at *P* < 0.05. For a description of this method, see a previous publication (Slotnick and Schacter 2004). Distinct activation related to the PPI was also examined by masking (excluding) the main effect of conflict-related activation with *P* < 0.05. fMRI results were mapped onto the surface of the cerebral cortex using Caret5 software (Washington University, <http://brainmap.wustl.edu>, Van Essen et al. 2001).

The coordinates of activation in standard Montreal Neurological Institute (MNI) ICBM152 space were transferred to Talairach space using a nonlinear transform (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>) for cerebral nomenclature according to an MRI atlas of the human brain (Talairach and Tournoux 1988). The ACC includes Brodmann's areas 33, 25, 24, and part of 32, and the posterior cingulate cortex (PCC) includes Brodmann's areas 23, part of 31, 30, 29, 26, and the retrosplenial cortex (Devinsky et al. 1995; Vogt et al. 1995). The cingulate subdivisions were labeled in this study as 2 subdivisions of the RCZ: RCZa and RCZp, and a CCZ, anterior and posterior to the vertical plane passing through the anterior commissure (VAC) according to the literature (Picard and Strick 2001). These approximately correspond to the anterior part of areas 24' and 32' (a24' and a32'), posterior part of area 24' (p24'), and area 24d, respectively, for the subdivisions according to the architecture of the macaque monkey and human cingulate cortex (Vogt et al. 1995; Bush et al. 2000; Paus 2001; Vogt et al. 2005).

We operationally defined the locations of the RCZa and RCZp as *y* = 23 ± 7 mm and *y* = 6 ± 9 mm (mean ± SD) relative to the VAC, respectively, based on functional activation related to conflict processing and response selection (Picard and Strick 2001). The location of CCZ was approximated as *y* = -11 ± 8 mm based on activation related to a motor task (Kwan et al. 2000). The region that we defined here as CCZ is wider and more posterior than what has been previously described (Picard and Strick 2001; Ridderinkhof et al. 2004). The coordinates of activation in

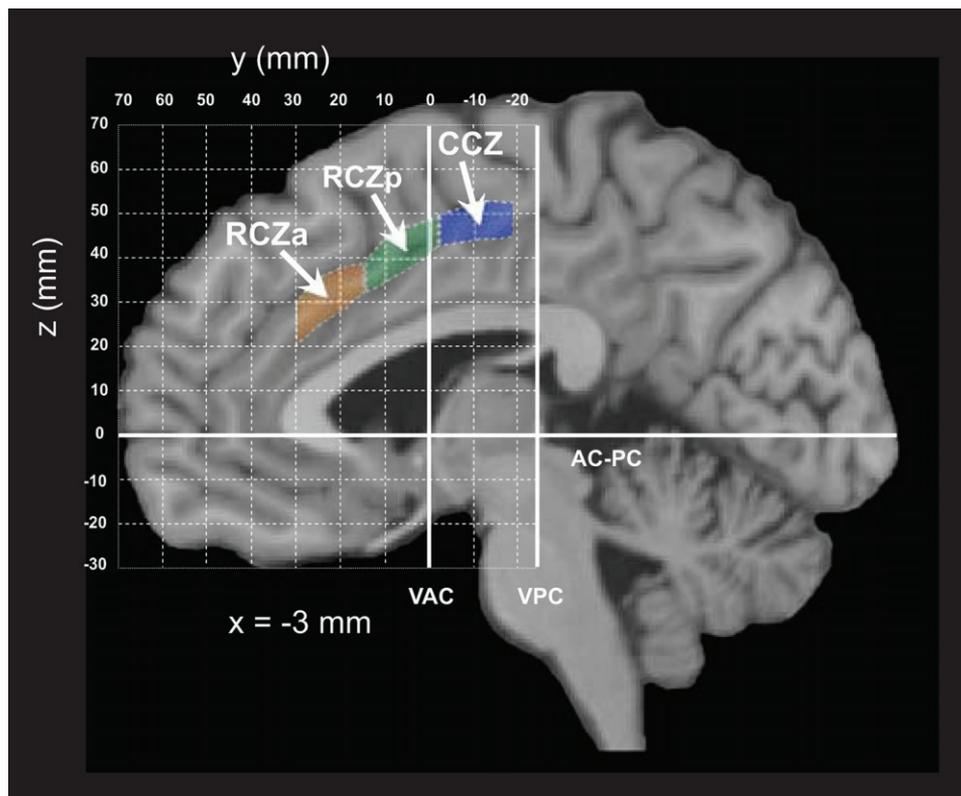


Figure 2. Operational definitions of the anterior rostral cingulate zone (RCZa), posterior rostral cingulate zone (RCZp), and caudal cingulate zone (CCZ) of the ACC.

Table 1

Regions with significant positive/negative PPI

Region	BA	MNI coordinates			Voxel	Z	P
		x	y	z			
<i>Positive</i>							
L CCZ ^a	24d	-18	-16	56	1346	3.84	0.000
R middle frontal gyrus	46	44	30	24	251	3.65	0.000
R precentral gyrus	6	36	2	14	471	3.47	0.000
L precentral gyrus	6	-40	4	20	254	3.13	0.001
L postcentral gyrus	3	-46	-22	50	189	2.89	0.001
L caudate nucleus		-20	-10	22	164	3.08	0.001
<i>Negative</i>							
R cuneus ^b	18/19	6	-74	8	414	-3.79	0.000

^aCCZ of the ACC. The activation extends into the dorsal part of the lateral premotor cortex (PMd, area 6) and the pre-SMA and SMAs.

^bCenters at the calcarine sulcus and extends into the cuneus and the PCC. BA, Brodmann's area; MNI, MNI ICBM152 space; voxel size is $2 \times 2 \times 2$ mm³.

Talairach space (Talairach and Tournoux 1988) were transferred to MNI space using a nonlinear transform (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispac.html>). The borders of these regions are presented graphically in Figure 2.

Dynamic Causal Modeling

Following identification of the key areas engaged in PPI, the next step was to characterize the network dynamics of these areas related to conflict processing. In order to draw inferences about the directionality of the interregional interactions, that is, the effective connectivity, DCM (Friston et al. 2003; Penny et al. 2004) was used with a hypothesis informed by the results of the PPI analysis. This DCM approach uses a dynamic input-state-output model, with multiple inputs and outputs, and with 1) parameters that mediate the influence of extrinsic inputs on the states (the C matrix), 2) parameters that mediate intrinsic coupling among the states (the A matrix), and 3) bilinear parameters (the B matrix) corresponding to PPIs in classic regression analysis, which allow the contextual inputs to modulate coupling. The outputs are hemodynamic responses that are transformed from state variables representing neuronal activity via a forward biophysical model. Interactions among the neuronal states of multiple interconnected regions in generating the observed hemodynamic response can be modeled explicitly by DCM. The effective connectivity revealed by DCM, which infers direction of neural influences, does not necessarily result from an explicit direct anatomical connection because DCM models the connections through the coupling of signal change among modeled regions (Mechelli et al. 2005; Booth et al. 2007; Sonty et al. 2007).

Subject-specific regions were selected for the modeling based on the group coordinates of the maxima of the SPM{F}, with significant positive and negative psychophysical interactions from the PPI analysis (listed in Table 1). As used by other studies (e.g., Smith et al. 2006), the subject-specific VOI, which was identified within each subject's activation map and was close to the group VOI, was extracted so long it was within 16 mm (with exceptions primarily in the motor cortices, where VOIs were within 26 mm), which is double the full-width-at-half-maximum of the smoothing kernel, of the random effect peak, and was within the same brain structure. The mean distance and standard deviation of the individual VOIs from the group maxima in Table 1 were 9 and 6 mm. Time series comprising the first eigenvariables of all voxels within a 6-mm radius sphere centered on the coordinates of the maxima of the SPM{F} in MNI space were extracted for these regions using $P < 0.05$ of target responses from the conventional SPM analyses, not PPI analysis, adjusted for cue and target effects of interest. The model structure, that is the connectivity pattern between regions, was predetermined based on our knowledge of anatomical connections. Constraints on highly unlikely intrinsic connections, either unidirectional or bidirectional, were imposed by setting their prior variance to zero (which is equivalent to setting the connection weight to zero). The cue (center and spatial, which were not the effect of interest in this report) and target (with congruent or incongruent flankers) driving inputs were modeled as the direct input to all modeled regions.

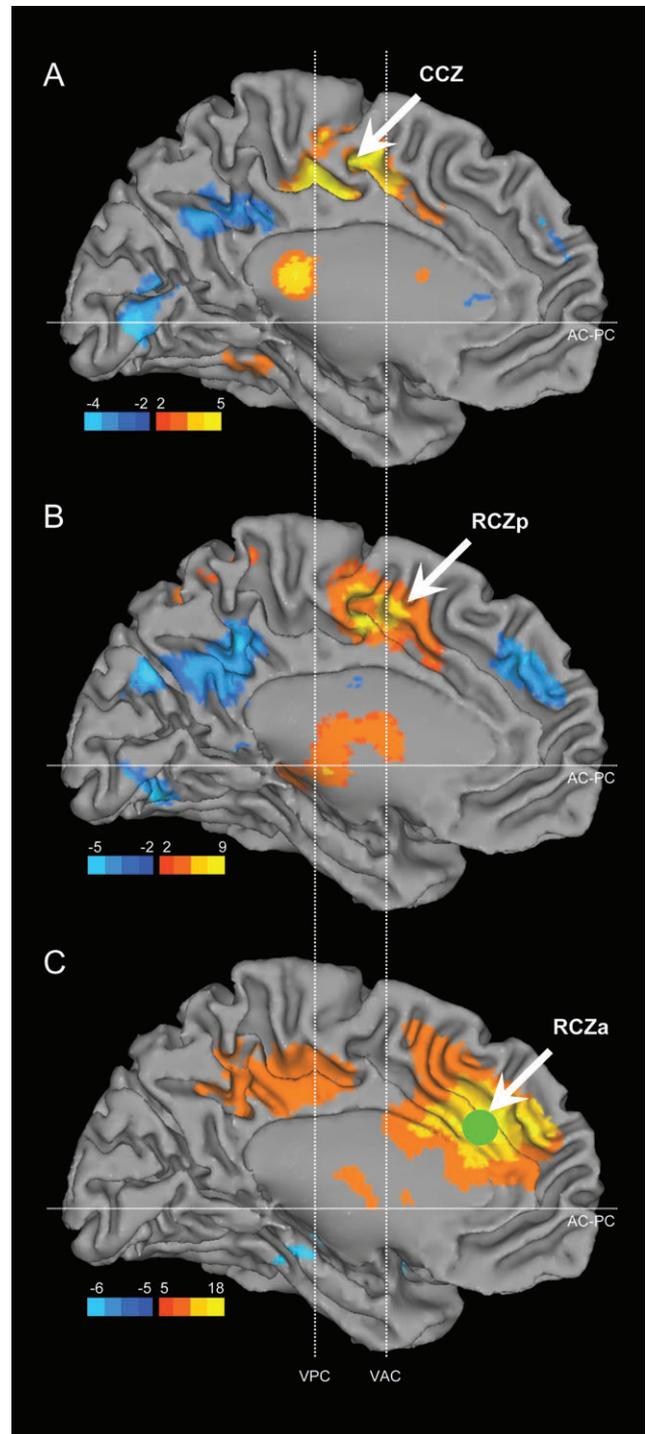


Figure 3. Surface map of the cerebral cortex of the PPI, conflict effect, and baseline connectivity of the ACC. (A) The PPI results, that is, brain regions with a steeper regression slope (orange to yellow color) or with a less steep slope (blue to light blue color) for ACC activity for target response with incongruent flankers than for target response with congruent flankers. (B) The main effect of greater (orange to yellow color) or less (blue to light blue color) activation for target response with incongruent flankers compared with congruent flankers. (C) The brain activity positively correlated (orange to yellow color) or negatively correlated (blue to light blue color) with the time course of the ACC VOI. The green dot in (C) represents the mean coordinates of ACC VOI as indicated in the method section. These 3 figures were thresholded with $P < 0.05$, $P < 0.05$, and $P < 0.0002$ (2-tailed), respectively. The color bars represent t values. VAC, vertical plane passing through the anterior commissure; VPC, vertical plane passing through the anterior commissure. AC-PC, line crossing anterior commissure-posterior commissure.

The intrinsic connection estimates represent the rate of change of neuronal activity in one area induced by activity in another area, and can be regarded as baseline connectivity established by the experimental context (Mechelli et al. 2004). In DCM, strong connection strength corresponds to a fast response with a small time constant. The conflict contextual modulatory input (when there is a target with incongruent flankers) was allowed to exert influences over the intrinsic connections, which were hypothesized to be modulated by the conflict context, by bilinear terms. The estimates of the intrinsic connections and the bilinear terms refer to the effective connectivity and the change in effective connectivity, respectively (Mechelli et al. 2005). Using an Expectation Maximization algorithm, models were evaluated separately for each run of each participant, by tuning the neurodynamic and hemodynamic parameters to minimize the discrepancy between predicted and observed BOLD signal (Ramnani et al. 2004). An aggregate DCM model across scan sessions for each subject was produced using Bayesian averaging. Finally, the intrinsic and bilinear parameters of each participant were entered into one-sample *t* tests for second-level population inference, as used by Mechelli et al. (2005). Because this study is hypothesis driven, Bonferroni correction for multiple comparisons was not conducted. The focus of our modeling was on whether the connection strength is modulated by the conflict context, but not on comparing different models representing competing hypotheses.

Results

As reported elsewhere (Fan et al. 2005), mean reaction time (RT) (and SD) was 717 ms (110) for the congruent condition and 818 ms (132) for the incongruent condition. A repeated measures analysis of variance on RT showed that the main effect of target condition was significant, $F_{1,15} = 50.86$, $P < 0.01$, indicating that a behavioral conflict effect did occur.

Figure 3 shows the significant PPI (Fig. 3A), the main effect of conflict (Fig. 3B), and the baseline connectivity of the ACC (Fig. 3C) projected onto a surface map of the cerebral cortex. The ACC activation (voxels above the threshold) was bilateral although the peak was lateralized and we only plotted the activation on the left hemisphere.

The PPI

The PPI represents the difference between the regression slopes of other regions' activity regressed on the ACC VOI activity for target responses with incongruent flankers and of that with congruent flankers. Figure 3A and Table 1 show brain regions with increased or decreased connectivity with the ACC VOI (see Fig. 3C). The ACC VOI (RCZa) showed increased conflict-dependent interaction with the CCZ, the right middle frontal gyrus (area 46) (Fig. 4), the left and right precentral gyri, the left postcentral gyrus, and the left caudate nucleus. The massive activation in the CCZ extends into dorsal lateral premotor cortex (PMd, area 6) and the SMA, the latter having *y*-coordinate ≤ 10 and *z*-coordinate ≥ 50 (Koski and Paus 2000). A negative interaction was found in the right cuneus extending into PCC.

We were unable to model error-trials in this analysis because error rate was very low (6%). To ensure that activation due to error-trials did not contribute to the results of the PPI analysis, we performed a voxel-wise second-level correlation analysis with PPI contrast estimate images regressed onto error rate. No region in which an interaction reached significance in the PPI random effects analysis bore a significant relationship to error rate.

The Main Effect of Conflict

The main effect of conflict is the difference between the amplitudes of the hemodynamic responses for the incongruent

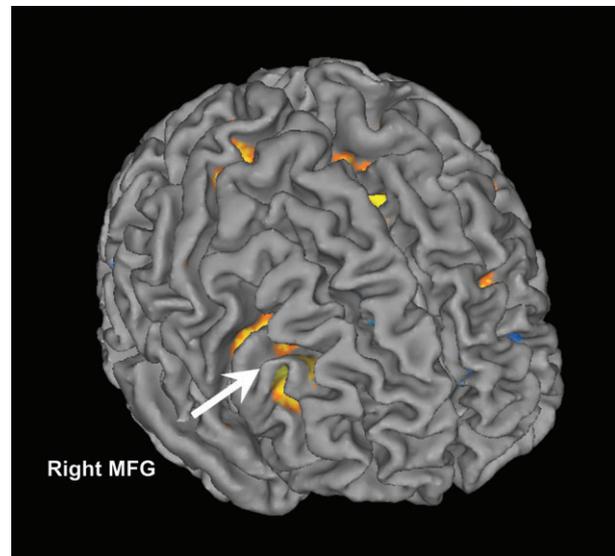


Figure 4. The PPI result of functional integration of ACC VOI (RCZa, shown in Fig. 2C) with right middle frontal gyrus (MFG) during conflict processing.

Table 2

Regions with significant activation/deactivation for the main effect of conflict

Region	BA	MNI coordinates			Voxel	Z	P
		x	y	z			
<i>Positive</i>							
L RCZp ^a	p24'	-6	-8	50	5109	5.25	0.000
R inferior frontal gyrus	44	60	6	26	1790	4.62	0.000
R superior parietal lobule ^b	7	32	-54	46	2988	4.48	0.000
L fusiform gyrus	37	-46	-60	0	388	3.38	0.000
L insula		-34	16	8	458	3.33	0.000
L postcentral gyrus	40	-54	-24	20	129	3.15	0.001
R thalamus (pulvinar)		20	-26	2	2425	4.39	0.000
<i>Negative</i>							
R precuneus ^c	7	14	-50	38	1122	-3.90	0.000
R superior frontal gyrus	9	10	44	30	1050	-3.69	0.000
R lingual gyrus	18	18	-76	-6	1006	-3.64	0.000
R insula		38	-36	20	118	-2.63	0.004

^aRCZp of the ACC. The activation extends into the posterior part of area 24' (p24') and peaks the area 6. That is, though the local maxima is at the CCZ, the cluster covers the area of RCZp.

^bDenotes the cortex along the intraparietal sulcus.

^cExtends into the PCC.

and for the congruent conditions. Figure 3B and Table 2 show regions with significant increased or decreased activation for target responses with incongruent flankers compared with congruent flankers, when controlling for the baseline activity of ACC VOI (RCZa). There was a region of greater activation centered in the RCZp and the pre-SMA/SMA. There was some overlap between the PPI and conflict main effect maps in the ACC. However, the central location of the medial frontal region activation was slightly anterior and inferior compared with the PPI result (*y* = -8 vs. -16, *z* = 50 vs. 56) and the distance between the 2 centers of mass was 16 mm. Though the local maxima is at the CCZ according to our operational definition, the cluster covers the area of RCZp. The distinct activations in divergent ACC subdivisions related to PPI and the main effect of conflict processing were confirmed by using activation related to one of the 2 processes as a mask to exclude the regions of common activation. It is worth noting that other regions, especially the cortex along the intraparietal sulcus, the right inferior frontal

gyrus, the pulvinar nucleus of the thalamus, and the left fusiform gyrus, were associated with the main effect of conflict. There was also deactivation in the right precuneus extending into the PCC, the right superior frontal gyrus, the right lingual gyrus, and the right insula cortex.

We also correlated contrast estimate maps representing the main effect of incongruent-congruent with subjects' error rates, and found significant positive correlations in the PCC and precuneus. This demonstrates that increased activity in these structures during conditions of high conflict was associated with increased error rate.

The Baseline Connectivity of the ACC VOI

The ACC VOI served as the seed region and the control for whole-brain overall activity in the PPI analysis by using a general linear model (GLM) to regress the whole brain's BOLD response on the ACC VOI's BOLD response. This method is essentially equivalent to that used in examining functional connectivity, which is typically calculated as the temporal correlation

between the activity of a VOI and all other voxels or VOIs sampled in the brain (Bokde et al. 2001; McIntosh et al. 2003). Figure 3C and Table 3 show brain activity positively or negatively correlated with the ACC VOI activity. The center of mass of the RCZa activation was at the center of the seed VOI and was much more anterior compared with the ACC activation related to the PPI (CCZ, Fig. 3A) and conflict processing (RCZp, Fig. 3B). This suggests an anatomical dissociation among the general functional connectivity of the ACC, the PPI, and the main effect of conflict processing. Extensive activity in the whole brain can not be seen in Figure 3C because we used a more restricted threshold ($P < 0.0002$) to demonstrate the ACC peak activity. There was massive activation associated with the ACC VOI (RCZa) activity in the whole brain, accounting for about one third of the whole-brain gray matter volume compared with the averaged gray matter volume from a previous study (Gur et al. 1999). A negative functional connectivity was found in the right cerebellum and the right superior temporal gyrus.

The Dynamic Causal Relationship

Figure 5 shows a probable architecture with specification of intrinsic and modulatory connections. The model consisted of the ACC VOI (RCZa) and the 7 regions activated by the PPI (see Table 1), including CCZ, PCC and right cuneus, left caudate nucleus, right middle frontal gyrus, left precentral and postcentral gyri, and right precentral gyrus. Because the activation of the left cuneus cluster extended to the PCC from the PPI analysis result, we combined these regions as one node and named it as "PCC and R Cuneus." The PCC serves as a relay for the reciprocal connections between CCZ and left cuneus. There were bidirectional intrinsic connections between the RCZa and the CCZ, the CCZ and the PCC, the RCZa and the right middle frontal gyrus, the CCZ and the left and right precentral gyri, and the left precentral gyrus and the left postcentral gyrus. The left caudate nucleus had unidirectional

Table 3
Regions with significant activation/deactivation associated with baseline activity of ACC

Region	BA	MNI coordinates			Voxel	Z	P
		x	y	z			
<i>Positive</i>							
R RCZa ^a	a24'/32' ^b	4	28	28	28230 ^c	7.05	0.000
L RCZa	a24'/32'	-16	32	24		6.77	0.000
L RCZa	a24'/32'	-9	34	28		6.75	0.000
<i>Negative</i>							
R cerebellum		14	-30	-18	4873	-5.02	0.000
R superior temporal gyrus	38	42	4	-20	373	-4.03	0.000

^aPeaks at the RCZa of the anterior cingulate gyrus.

^bAnterior part of areas 24' and 32'.

^cIncludes activated voxels of the RCZa of the left anterior cingulate gyrus.

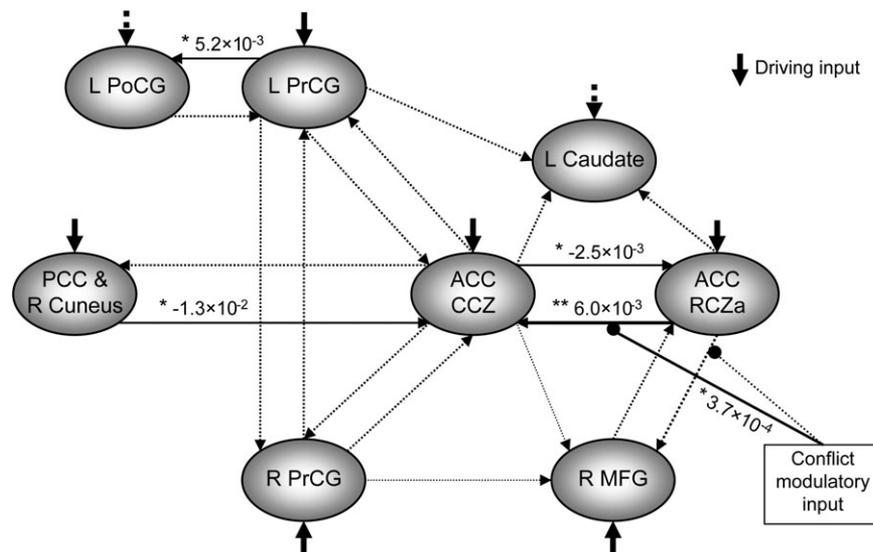


Figure 5. Functional architecture and results of the DCM analysis on effective connectivity. The cue and target driving input exerts influence on all VOIs. Intrinsic connections are shown as directed black arrows between 2 regions. The conflict modulatory input modulates the forward connections from the ACC VOI (RCZa) to the CCZ, and from the RCZa to the left MFG. The dashed, solid and thick solid lines represent theoretical but not significant, strong ($*P < 0.05$), and very strong ($**P < 0.01$) connections, respectively. The arrowheads with solid lines and dotted lines represent significant and nonsignificant driving inputs in a comparison of the incongruent and congruent conditions. The significant intrinsic and bilinear coupling estimates are shown alongside the corresponding connection, representing the connection strength (Hz). MFG, middle frontal gyrus; PrCG, precentral gyrus; PoCG, postcentral gyrus.

connections from the RCZa, the CCZ, and from the left precentral gyrus. The right middle frontal gyrus receives weak influence from the CCZ and the right precentral gyrus. The conflict context input was hypothesized to modulate the connectivity from the RCZa to the CCZ and from the RCZa to the right middle frontal gyrus.

The dashed, solid, and thick solid lines represent theoretical but not significant, strong ($P < 0.05$), and very strong ($P < 0.01$) connections, respectively. A positive intrinsic parameter indicates that increased (decreased) activity in the source region leads to increased (decreased) activity in the target region, whereas a negative intrinsic parameter indicates that increased (decreased) activity in the source region leads to decreased (increased) activity in the target region. The functional specification depends on the sign of both the forward and backward intrinsic connections (Mechelli et al. 2003). There was a positive forward intrinsic connection from RCZa to CCZ and a negative backward intrinsic connection, mediating a “gain control” mechanism. However, the magnitude of the positive value was greater than the negative one, resulting in a net excitatory effect of the RCZa on CCZ. The positive bilinear parameter of the modulation of conflict context on the connection from the RCZa to CCZ was also significant, indicating that the effective connectivity from the RCZa to CCZ was even stronger than baseline connectivity under the context of conflict. This relationship indicated that the slope of CCZ activity regressed on the RCZa activity in the PPI analysis was positive and was increased significantly during the context of conflict.

There was a significant intrinsic connection from the left precentral gyrus to the left postcentral gyrus, and a significant negative intrinsic connection from the PCC and right cuneus to CCZ. However, the intrinsic connection between the RCZa and the right middle frontal gyrus and the modulation of the conflict context on the connectivity from the RCZa to the right middle frontal gyrus were not significant. This was inconsistent with the PPI result and possibly related to the fact that the same driving inputs were modeled at each node, which reduces the variance in activity in a given node introduced by afferent connections. The lack of a significant intrinsic connection between the left precentral gyrus and the right precentral gyrus may be due to the fact that participants used either the left or right hands but not both, to make a response for a single trial.

We did not explicitly compare models to find the most plausible regions with driving inputs as done in a recent study of effective connectivity in target stimulus processing by Brazdil et al. (2007). In our model, all regions received a driving input. To explore the nature of the driving input, we calculated the difference of the inputs under incongruent and congruent conditions. The driving inputs with significant and nonsignificant differences are shown as arrowheads with solid and dashed lines, respectively. The driving input parameter of the C matrix for the extrinsic influence of input on RCZa was changed from -7.7×10^{-3} to -4.5×10^{-3} , and the increase was significant, $t_{(15)} = 2.12$, $P = 0.05$. All other significant inputs under conflict were positive. However, the difference was negative for the PCC and right cuneus, $t_{(15)} = -2.10$, $P = 0.05$, indicating that conflict-induced activation decreases in these regions.

Discussion

The PPI analysis largely confirmed previous findings of strong interconnections of the cognitive division of the ACC with the

lateral prefrontal cortex, premotor area, and SMA (Devinsky et al. 1995). Most importantly, the DCM pattern revealed significant effective connectivity from the RCZa to the CCZ of the ACC, and a significant modulation effect indicated that the contextual input of conflict generally enhances this effective connectivity. The strong correlation between the activity of caudal ACC and the lateral prefrontal cortex and motor/premotor areas is consistent with the macaque monkey literature (Morecraft and Van Hoesen 1992; Bates and Goldman-Rakic 1993; van Hoesen et al. 1993), as well as with the meta-analysis of functional connectivity of the ACC within the human frontal lobe (Koski and Paus 2000). The finding of strong connectivity between the RCZa and the middle frontal gyrus (area 46) from the PPI analysis supports the greater-than-chance frequency of concomitant activation of the ACC and middle frontal gyrus reported in another meta-analysis (Koski and Paus 2000). The strong negative connectivity centered in the right cuneus, which extended to the PCC (areas 23 and 31), has also been implicated in the “task-negative” network during attention demanding cognitive tasks (Fox et al. 2005). The observed integration of the RCZa and the right middle frontal gyrus, left and right precentral gyri, left caudate nucleus, and left postcentral gyrus may reflect the underlying mechanism of functional networks of these regions for response execution during conflict processing. The results of this study support the hypothesis that conflict processing is associated with an increase of effective connectivity between the cognitive division of the ACC and remote regions of the brain to facilitate selection and response execution.

The regions activated by the main effect of conflict in the present analysis overlap to some extent with regions of activation reported in our previous study (Fan et al. 2005). For example, the thalamus (pulvinar) and left fusiform gyrus activations have similar coordinates as in our prior study. However, there are also some discrepancies, which may stem from the use of different modeling methods. The present analysis utilized 3 regressors: one for the interaction, one for the conflict effect, and one for baseline time course, in contrast to 2 regressors, each for the congruent condition and incongruent conditions, as in our previous conventional analysis (Fan et al. 2005). The present analysis investigated the experimental manipulation on the network dynamics, specifically the contribution of the activity of the anterior rostral ACC VOI (RCZa) to the activity of other regions during conflict processing. The activation found in RCZp appeared when baseline activity of ACC VOI was controlled for.

The present data also reveal the intrinsic dynamic organization of anticorrelations among networks. fMRI studies in which experimental conditions are compared with baseline rest or simple sensory processing often report deactivation of the PCC (Shulman et al. 1997). Indeed some structures can be metabolically more active during the resting state; it has been suggested that activity in these structures represents a “default mode” of brain function (Raichle et al. 2001). Two networks exhibiting anticorrelated activity have been defined in studies of functional connectivity patterns (Greicius et al. 2003; Fox et al. 2005). One of the 2 broadly defined networks incorporated structures commonly activated by cognitive tasks and the other incorporated structures commonly exhibiting “deactivation” in fMRI and PET studies when cognitive tasks are compared with resting baselines. The former “task-positive” network included structures such as the cortex along the intraparietal sulcus, frontal

eye field, insula, and SMA, and the later “task-negative” network included structures implicated in the “default state” network, including the medial prefrontal cortex (area 32/10), the PCC, and the precuneus.

In the current study, the conflict-related deactivation in the precuneus extending to the PCC and in the medial prefrontal cortex exhibited the same pattern as the anticorrelated activity in PCC and medial prefrontal cortex during attention demanding cognitive tasks (Fox et al. 2005), and the opposite pattern as the resting-state activity in PCC/precuneus (Greicius et al. 2003). For the incongruent condition in which a high degree of conflict was present, we found increased activation in the RCZp and deactivations in the PCC, and significant negative intrinsic connectivity from the PCC to the CCZ. There was a negative correlation between activation of the intraparietal cortex and the PCC, as reported earlier (Fox et al. 2005). We reasoned that activation in regions that are a part of this “default-mode” network might represent diminished attention to the task and thus should correlate with error rate. We found that there was a significant positive correlation between subjects’ error rate and activation in the PCC (and precuneus) and intraparietal cortex. These results, together with the finding of an anatomical connection between areas 24 and 23 in macaque monkeys (Vogt and Pandya 1987) make the existence of a homologous, inhibitory connection in humans a plausible assumption.

For the ACC VOI baseline time course, the BOLD signal for the spontaneous functional activity found in the ACC and several other regions may indicate an overall change of ACC and whole-brain activity evoked by state changes, such as fixation periods versus response periods. The oscillatory neuronal activity may play a role in facilitating the coordination and organization of information processing spatially and temporally as proposed by Raichle and Mintun (2006). ACC activity is also possibly modulated by cue conditions in the ANT related to response anticipation and preparation (Fan et al. 2007). The maximum positive peaks were within the ACC but the maximum negative peaks were in the right cerebellum and right superior temporal gyrus. The SPM software package defines only 3 maximum peaks within each cluster. If we change this default, we may find more peaks in other regions. For example, the PCC would be one of these. Other factors such as global mean signal change and head motion may drive the massive “activation,” although we used global mean and motion correction parameters in the modeling as covariates of no interest in the first-level GLM, as it has been suggested that inclusion of these covariates is generally useful for increasing the sensitivity of GLM in the analysis of event-related fMRI (Johnstone et al. 2006).

The ACC VOI, which is located 32 mm anterior to the VAC, is located in the RCZa, whereas the main effect of conflict-related activation and the interaction, which both exhibit peaks -8 mm and -16 mm posterior to the VAC but extended anteriorly, is close to the RCZp and the CCZ, respectively. This result is consistent with the theory that conflict processing is linked to the RCZa, response selection is linked to the RCZp, and movement execution is linked to the CCZ (Picard and Strick 2001). The functional separation of ACC subdivisions found in this study may support an integration of the theories of conflict monitoring (Botvinick et al. 1999) and attention/selection for action (Petersen et al. 1988), suggesting that activation of ACC and other brain regions including subdivisions of ACC occur due to conflict processing (Fan, Flombaum, et al. 2003).

The common goal of our PPI and DCM analyses was to determine how the contribution of activity in the ACC to activity in other structures changed under conditions of conflict. First consider the PPI analysis. Because the slope of the regression of CCZ activity on RCZa activity was greater during conditions of conflict compared with conditions of no conflict (i.e., there was a significant positive interaction between the psychological variable of level of conflict and the physiological variable of RCZa activity) we conclude that the context of conflict positively modulates the strength of the connection between the RCZa and CCZ. The same conclusion can be reached, though via different computational means, using DCM. DCM utilizes forward biophysical models of neuronal activity to estimate the HRF output. The contribution of activity in one region to another is modeled as the effect that neuronal activity in one region has on the rate of change of neuronal activity in another. The DCM analysis complimented the PPI analysis in that, though there was strong intrinsic connectivity between RCZa and CCZ (analogous to a positive slope of the regression of CCZ activity on RCZa activity without the context of conflict), the context of cognitive conflict further increased the strength of this influence (analogous to an even steeper positive slope of the regression line). Although DCM provides support for PPI results, it confers further advantage by permitting the modeling of bidirectional influences between a manageable number of nodes and thus hypothesis-driven network analysis.

There are some limitations in the DCM of the current design. The conflict effect was used as both a driving input and modulator. As suggested by Klass E. Stephan in the SPM discussion listserv, use of the same input as a driving input to one region and as a modulator of an afferent connection originating in that region may result in overestimation of the driving parameters and underestimation of the modulatory parameters, due to the fact that the conditional estimates of both parameters will be highly correlated and the prior variance for driving inputs will be higher than modulatory ones. Assuming that a typical regional activity has a time constant in the order of 1–2 s (1–0.5 Hz) (Noppeney et al. 2006), the modulatory effect of 3.7×10^{-4} Hz of conflict on the connection between RCZa and CCZ was relatively very small, although statistically significant. This might also be related to the fact that the experimental design was rapid event-related, and the short duration of the events and the low signal-to-noise ratio of the hemodynamic response may have reduced the size of the effect. These factors underlying the relatively small intrinsic connectivity between the RCZa and CCZ and modulation effect may also explain why the findings between the RCZa and right MFG did not reach significance, given that the right MFG *z*-score, though relatively high in the PPI analysis, was still weaker than that of the CCZ. Finally, although we selected regions based on the PPI analysis to represent the PPI related network, we had to use cue events as input in order to optimize model fitting in the DCM analysis, thus the intrinsic connectivity data may also reflect intrinsic connectivity due to the cue event, and not purely the target event itself. However, this may reflect the dynamic nature of the modeled regions such that they are involved in more than one cognitive function (Fan et al. 2007).

In summary, we found that the RCZa, RCZp, and CCZ of ACC, as well as the middle frontal gyrus, primary and SMAs, and other regions implicated in the processing of conflict. Considering the anatomic connections of the ACC and prefrontal regions, the

results of this study were not unexpected. However, whereas anatomical connectivity is fixed, functional and effective connectivity are task and context dependent. The current analysis allowed us to move beyond the establishment of structure–function correlations provided by the traditional GLM analysis. By examining the PPI, we were able to determine what structures share effective connections with the ACC. By then excluding structures that were merely correlated with task demands, we were able to form a hypothesis of patterns of interconnectivity of the executive control of attention network. The finding of significant modulation of certain connections under conditions of conflict using DCM allowed us to form a structure–function relationship by mapping the function of conflict processing onto the identified network. The results suggest that the activation in the ACC is widely distributed and that several major parts of the ACC work together and with some other brain areas to resolve the conflict.

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