Separable responses to error, ambiguity, and reaction time in cingulo-opercular task control regions

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ABSTRACT

The dorsal anterior cingulate (dACC), along with the closely affiliated anterior insula/frontal operculum, have been demonstrated to show three types of task control signals across a wide variety of tasks. One of these signals, a transient signal that is thought to represent performance feedback, shows greater activity to error than correct trials. Other work has found similar effects for uncertainty/ambiguity or conflict, though some argue that dACC activity is, instead, modulated primarily by other processes more reflected in reaction time. Here, we demonstrate that, rather than a single explanation, multiple information processing operations are crucial to characterizing the function of these brain regions, by comparing operations within a single paradigm. Participants performed two tasks in an fMRI experimental session: (1) deciding whether or not visually presented word pairs rhyme, and (2) rating auditorily presented single words as abstract or concrete. A pilot was used to identify ambiguous stimuli for both tasks (e.g., word pair: BASS/GRACE; single word: CHANGE). We found greater cingulo-opercular activity for errors and ambiguous trials than clear/correct trials, with a robust effect of reaction time. The effects of error and ambiguity remained when reaction time was regressed out, although the differences decreased. Further stepwise regression of response consensus (agreement across participants for each stimulus; a proxy for ambiguity) decreased differences between ambiguous and clear trials, but left error-related differences almost completely intact. These observations suggest that trial-wise responses in cingulo-opercular regions monitor multiple performance indices, including accuracy, ambiguity, and reaction time.

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Introduction

Much of cognitive neuroimaging research begins from a search for a single explanation for processing within a specific cortical region. This approach has certainly been prevalent in the case of response in the dorsal anterior cingulate (dACC), which in the broad literature extends dorsal to the medial superior frontal cortex (dACC/msFC).

Many explanations for the trial-related responses in dACC/msFC have been offered. It has often been suggested that these responses are related to accuracy or error probability. For example, work in our own lab has shown that the dACC/msFC has demonstrated greater activity to errors than correct trials, across multiple tasks (Dosenbach et al., 2006, 2007; see also Emeric et al., 2008; Ito et al., 2003). On the other

hand, many studies have been interpreted to suggest that dACC/msFC activity is related to processes associated with decision uncertainty. In one line of work, the dACC/msFC appears to show responses to ambiguity in semantic (Thompson-Schill et al., 1997), visual motion (Sterzer et al., 2002), and face processing paradigms (Demos et al., 2004), as well as ambiguity in emotion (Neta et al., 2013). Similarly, the dACC/msFC has been widely thought to respond more in situations of conflict (Botvinick et al., 1999, 2001; Carter et al., 1998; MacLeod and MacDonald, 2000), particularly when the task requires a response relevant to that conflict (Milham et al., 2001). Indeed, many studies that have examined ambiguity and conflict have described them as a co-activation and/or selection among competing response options (Botvinick et al., 2001; Milham et al., 2001; Sterzer et al., 2002; Thompson-Schill et al., 1997; see Grinband et al., 2011). Still other research has shown that when reaction time is accounted for, some of these processing distinctions (error, conflict/ambiguity) appear minimal or absent (Grinband et al., 2011). This work argues that the cingulate region is associated with a process primarily modulated by

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reaction time (e.g., sustained attention, effort, working memory), with slower reaction times (i.e., more time on task) eliciting greater activity.

Much of the preceding work has also suggested a high degree of similarity in the activation of the bilateral anterior insula/frontal operculum (aI/fO) in many of these tasks. For example, this region shows a response similar to the dACC/msFC in response to error (Dosenbach et al., 2006), perceptual recognition (Ploran et al., 2007), and a wide variety of other manipulations of conflict, error, and uncertainty (e.g., Grinband et al., 2006; Nee et al., 2011; Wessel et al., 2012; Wheeler et al., 2008), as well as ambiguity (Demos et al., 2004; Neta et al., 2013; Sterzer et al., 2002; Thompson-Schill et al., 1997). Moreover, resting state functional connectivity shows strong and significant correlations between the bilateral aI/fO and dACC/msFC activity (Dosenbach et al., 2007), suggesting that they comprise the core of a larger "cingulo-opercular" system. Taken together, these effects provide further support for the notion that these regions, and their processing contributions, should be considered in concert.

The role of cingulo-opercular regions in task control

Interestingly, the trial-related signals described here and in many other studies are not the only responses attributed to the cingulo-opercular regions. Mixed block/event-related designs (see Fig. 1) that can model both sustained and transient signals during a task have been used to demonstrate that these regions show three distinct task-control signals across a wide variety of tasks. In addition to transient, trial-related signals described above, which we associate with performance feedback, there is (2) a transient start signal at the beginning of a task block, which may include signals related to the loading of task parameters, and (3) a sustained signal across an entire task block, presumably related to task maintenance. Thus, among potential other processes, these regions are thought to be involved in controlling goal-directed behavior including the stable maintenance of task set (see Dosenbach et al., 2008 for a review). Therefore, we suggest that any trial-related effects that are attributed to these regions (e.g., error-related activity, conflict) should fit into a greater model of how these regions relate to task control. It should be noted that the cingulo-opercular network is not the only network attributed to task control (e.g., frontoparietal). Importantly, previous work has argued that the cingulo-opercular network is responsible for task control operations that are distinct from the frontoparietal network (Dosenbach et al., 2006, 2007, 2008). In particular, in the context of broad task control (which includes all three signals mentioned above), we have shown that the cingulo-opercular network might be more useful for stable task maintenance, whereas the frontoparietal network is more useful for online adaptive control. Moreover, we have found that the transient signals in the cingulo-opercular network come online at or near the end of the trial, suggesting that these responses serve as feedback into the task set, whereas the signals in the frontoparietal network effects begin early in the trial and may be more related to accumulating information over the course of the trial (Ploran et al., 2007). Further, the error-related signals in the frontoparietal regions and cingulo-opercular regions have different temporal characteristics (e.g., Wheeler et al., 2008). Because of these a priori reasons to believe that these

networks represent distinct mechanisms of task control, we are motivated here to examine not the control signals of each mechanism, but rather we focus on the nature of the signals in cingulo-opercular regions, in particular as they are related to performance feedback.

Importantly, given that much of the preceding thought on cingulo-opercular regions has been directed at rationalizing a single explanation for error-related and uncertainty-related activity, a primary goal of the present work was to compare the neural signatures of trial-related responses in these regions (while also considering reaction time effects), in order to determine whether they are the result of one generic computation or, instead, resulting from multiple different computations. Moreover, we aim to demonstrate the generalizability of these effects across task contexts. To this end, we used two tasks in which there are both ambiguous and clear (i.e., unambiguous) trials, and in which participants also made errors. Specifically, we asked participants to make abstract/concrete judgments about English nouns (semantic task), as well as rhyming judgments about English word pairs (phonological task). We predict that, similarly for both tasks, there will be separable neural signatures for the three trial-related responses tested here: errors, uncertainty/ambiguity, and reaction time.

Methods

Participants

Forty healthy participants (right-handed, without neurological disease and with normal/corrected vision, 19 female, ages 21–30 years) volunteered. None were aware of the purpose of the experiment, and all compensated for their participation through monetary payment. Written informed consent was obtained from each participant before the session. All procedures were approved by the Washington University Committee for the Protection of Human Subjects. Two participants were excluded due to non-normative ratings (e.g., more than 40% of clearly concrete items were classified as abstract), which made it difficult to know if participants confused the button assignments (and thus, the ratings of ambiguity might have also been incorrect). A third participant was excluded because they only made responses on 80% of the total trials (including only 50% of the ambiguous trials), and four participants were removed due to motion-related artifacts (one of whom also had a low behavioral response rate). As a result, the final sample for behavioral analyses contained 37 participants (18 females), and the final sample for fMRI analyses contained 34 participants (16 females).

Task/stimuli

For both tasks, the words were largely chosen from the English Lexicon Project (Balota et al., 2007).

Semantic task

For the semantic task, we used 250 English nouns. All words were equated for frequency (HAL units, as reported from the English Lexicon Project database) across condition (mean ± SEM: abstract = 10,940.5 ± 1366; ambiguous = 25,516.2 ± 6382; concrete = 8947 ± 1245). Words were recorded by a female experimenter, and saved as individual sound files, using Audacity software (http://audacity.sourceforge.net/).

Phonological task

For the phonological task, we used 250 English word pairs, with one word presented above the other. Words were equated for length (mean ± SEM: rhyme = 5.6 ± .13; ambiguous = 5.6 ± .21; no rhyme = 5.4 ± .14) and frequency (HAL; mean ± SEM: rhyme = 17,107.0 ± 3008; ambiguous = 22,722.8 ± 7469; no rhyme = 23,433.0 ± 8780) across condition.
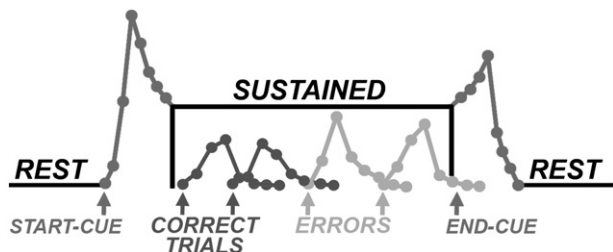

Fig. 1. A diagram of the trial structure in the mixed block/event-related design.

Pilot

In a behavioral pilot, we recruited a total of 33 participants (20 female) over the course of five experiments, where each person participated in only one of the five versions. In the first three versions of the pilot, each participant performed the semantic task on 240 single words and the phonological task on 240 word pairs. In the fourth version, each participant performed only the semantic task on 410 single words, and in the last version, each participant performed the semantic task on 298 single words and the phonological task on 240 word pairs. Each version of the pilot included some unique stimuli, and some repeated stimuli from previous versions. The methods for each version were the same as in the final experiment, except that there were more trials per block in the pilots in order to account for the additional stimuli. From these data, we identified ambiguous items based on response consensus (for details, see the end of the Procedure described below for the imaging study). We selected 250 words: 100 clearly abstract, 100 clearly concrete, and 50 with ambiguous concreteness (i.e., chosen because they had the highest standard deviation in ratings across participants, i.e., lowest response consensus), and 250 word pairs: 100 clearly rhyming, 100 clearly not rhyming, and 50 with ambiguous rhyming (again, chosen because they had the highest standard deviation in ratings across participants).

Procedure

The fMRI paradigm consisted of ten runs of two experimental blocks each: one block for each of the two tasks, in an interleaved order. Each block began with a brief (4 s) instruction screen, with the words ABSTRACT and CONCRETE, or the words RHYME and NO RHYME. The instruction screen informed each participant not only which task they were about to perform, but also how to respond (i.e., if the word ABSTRACT appeared on the left side of the screen, and CONCRETE on the right, participants were to press the left button to rate the words as abstract, and the right button to rate the words as concrete). The side of the screen was the same for each task block within participants, but was counterbalanced across participants.

In each block for the semantic task, 25 words were presented auditorily, 10 from each clear condition (abstract, concrete), and 5 from the ambiguous condition. Each word was presented, in a randomized fashion for all conditions, with an intertrial interval (ITI) that ranged approximately from 500 – 5500 ms (average = 3000 ms), during which a white fixation cross appeared on the screen (Fig. 2).

In each block for the phonological task, 25 word pairs were presented visually, 10 from each clear condition (rhyme, no rhyme), and 5 from the ambiguous condition. Each word pair was presented, in a randomized fashion for all conditions, for 2000 ms, with the same intertrial interval (ITI) that ranged from 500 – 5500 ms (average = 3000 ms). The order of the runs was counterbalanced across subjects, such that half of the participants performed the semantic task first, and the other half performed the phonological task first. Psyscope X was used for stimulus presentation and data collection (Cohen et al., 1993; http://psy.ck.sissa.it).

During imaging, subjects responded by pressing one of two buttons with their dominant hand. These responses were coded as 0 and 1, with an arbitrary assignment for each task, such that, for the semantic task, an "abstract" rating was coded as 1, and "concrete" as 0, and for the phonological task, a "no rhyme" rating was coded as 1, and "rhyme" as 0. Importantly, these values were then used to redefine ambiguity based on these 37 participants. In an item analysis, we averaged ratings across all participants, assigning a value to each stimulus that ranged from 0 to 1. Stimuli that had an average rating that was greater than 0.2, but less than 0.8, were considered to be ambiguous (i.e., participants were not in agreement in their ratings). We define this variable as response consensus, where words with 80% or greater consensus (i.e., on the extreme end of the scale: 0–0.2, 0.8–1) were categorized as clear, and those with less than 80% response consensus were categorized as ambiguous. In other words, response consensus simply serves as a measure for quantifying ambiguity across items. As such, in the semantic task, there were 100 clearly abstract, 97 clearly concrete, and 53 words that were ambiguous (e.g., CHANGE; 27% of trials were ambiguous; see Inline Supplementary Table S1). In the phonological task, there were 96 clearly rhyming pairs, 74 clearly not rhyming, and 80 words that were ambiguous (e.g., BASS/GRACE; 47% of trials were ambiguous; see Inline Supplementary Table S1). While this categorization based on our MRI participants differed from our original categorization using the pilot data, the differences in response consensus between the two groups were slight ($r = .95$).

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

Imaging acquisition

Data were acquired on a Siemens 3 T Trio scanner (Erlanger, Germany) with a 12-channel Siemens Matrix head coil. To help stabilize head position, each subject was fitted with a thermoplastic mask fastened to holders on the head coil. A T1-weighted MPRAGE structural image was obtained (slice time echo = 3.08 ms, TR = 2.4 s, inversion time = 1 s, flip angle = 8°, 176 slices, $1 \times 1 \times 1$ mm voxels). All
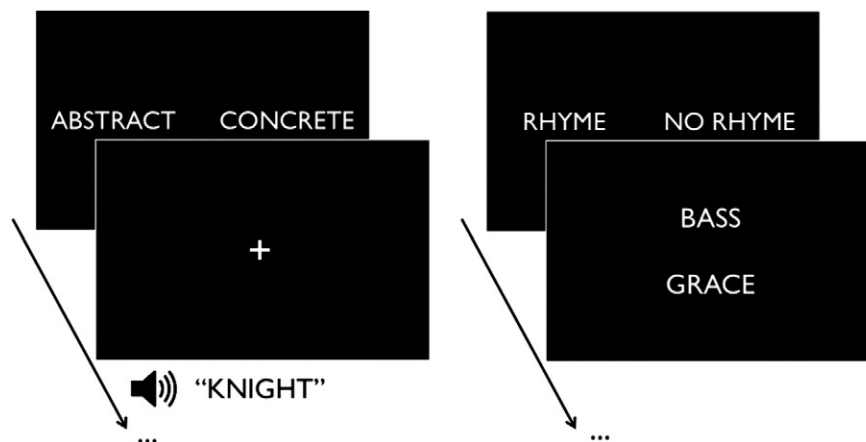

Fig. 2. The experimental paradigm. Each block began with a brief instruction screen, with the words ABSTRACT and CONCRETE, or the words RHYME and NO RHYME. In each block for the semantic (S) task, 25 words were presented auditorily, 10 from each clear condition (abstract, concrete), and 5 from the ambiguous condition. Each word was presented, in a randomized fashion for all conditions, with an intertrial interval (ITI) that ranged approximately from 500 – 5500 ms (average = 3000 ms), during which a white fixation cross appeared on the screen. In each block for the phonological (P) task, 25 word pairs were presented visually, 10 from each clear condition (rhyme, no rhyme), and 5 from the ambiguous condition. Each word pair was presented, in a randomized fashion for all conditions, for 2000 ms, with the same intertrial interval (ITI) that ranged from 500 – 5500 ms (average = 3000 ms).

functional runs were acquired parallel to the anterior–posterior commissure plane (TE = 27 ms; volume TR = 2.5 s, flip angle = 90°, in-plane resolution = 4 × 4 mm), using a blood oxygen level-dependent (BOLD) contrast-sensitive asymmetric spin-echo echo-planar sequence. Whole-brain coverage was obtained with 32 contiguous interleaved 4 mm axial slices. Steady-state magnetization was assumed after 4 frames. An auto-align pulse sequence protocol provided in the Siemens software was used to align the acquisition slices to the anterior and posterior commissure (AC-PC) plane and centered on the brain. A T2-weighted turbo spin-echo structural image (TE = 84 ms, TR = 6.8 s, 32 slices with 1 × 1 × 4 mm voxels) was also obtained in the same anatomical plane as the BOLD images to improve alignment to the atlas.

Imaging analysis

Preprocessing

Imaging data from each subject were preprocessed to remove noise and artifacts, including (a) correction for movement within and across BOLD runs using a rigid-body rotation and translation algorithm (Snyder, 1996), (b) whole brain intensity normalization to a common mode of 1000 to allow comparisons across subjects (Ojemann et al., 1997), and (c) temporal realignment using sinc interpolation of all slices to the temporal midpoint of the first slice, accounting for differences in the acquisition time of each individual slice. Functional data were then resampled into 2 mm isotropic voxels and transformed into stereotaxic atlas space (Talairach and Tournoux, 1988). Atlas registration involved aligning each subject's T1-weighted image to a custom atlas-transformed (Lancaster et al., 1995) target T1-weighted template using a series of affine transforms (Fox et al., 2005; Michelon et al., 2003).

Modeling sustained and transient signals in a mixed-design

BOLD activity related to the trials, start/stop cues, and task periods were modeled using the general linear model (GLM). Additionally, baseline and trend-effect terms for each BOLD run were included in the GLM. Effects were coded according to the same principles for all task conditions. Sustained set maintenance-related activity during trial performance was modeled with a square wave, starting eight frames after the beginning of each task block and terminating at the end. In addition, eight types of event-related activity were modeled using a stick function at the beginning of each event and for the subsequent eight scans (see Fig. 1). This approach makes no assumptions about the shape of the BOLD response, but does assume that all events included in a category are associated with the same BOLD response (Friston et al., 1994; Josephs et al., 1997; Miezin et al., 2000; Ollinger et al., 2001; Wheeler et al., 2006; Worsley et al., 1995; Zarahn et al., 1997a,b). Thus, we could extract timecourses without placing constraints on their shape. Image processing and analyses were carried out using in-house software written in IDL (Research Systems, Inc.). The eight events we modeled were the start-cue, the stop-cue, and three types of trials for each task (clear/correct, clear/errors, and ambiguous). As a result, we could summarize the maintenance-related activity with a single parameter (not discussed in the present paper) and each transient with eight parameters. The task-related transient parameters (i.e., event types: clear/correct, clear/errors, and ambiguous) were taken to a second level for random-effect analysis using f tests. A significant main effect of time (ANOVA) indicated that the hemodynamic response was different from flat across eight TRs. Individual subject data were transformed into the stereotactic space of Talairach and Tournoux (1988).

In the event type × time ANOVA, we included two behavioral regressors in a stepwise fashion. Because we had a priori reasons to believe that reaction time accounts for many of the response signals attributed to the dorsal cingulate (Grinband et al., 2011), we first regressed out reaction time effects. This regression was done on the single subject level by including a value for reaction time for each trial in the GLM for each subject. Next, we computed the residuals from this model and included them in a subsequent analysis where we included response consensus (see Procedure) as a regressor. Again, this regression was done on the single subject level, where the response consensus value for each item was entered into the GLM for each subject. For example, in the semantic task, the ambiguous item "SAFE" had a response consensus of 61%, whereas the clear item "ANXIETY" had a response consensus of 100%. These values, ranging from 50 – 100% were entered for each item in the model for each subject. As with the reaction time regressor, the response consensus regressor had one value for each trial (again, based on the item that was presented on that trial) that went into the GLM for each subject. The regressor for reaction time was scaled by subtracting the mean and dividing by the standard deviation across all trials, and the regressor for response consensus was scaled by subtracting the mean across all trials, which made the values for each regressor centered at zero. Each of these two (reaction time and response consensus) behavioral regressors contributed 8 columns to the design matrix, one for each frame of the BOLD response. Finally, because there is a relationship between our condition of interest (event type) and reaction time (i.e., reaction times were longer for clear/errors and ambiguous trials as compared to clear/correct trials), we redid this analysis with a reaction time regressor that was scaled by condition. Specifically, we calculated the average reaction time for each condition, and then subtracted that average from the value for each trial, according to the condition of the given trial. As a result, the average reaction time *for each condition* is 0.

Regions of interest (ROIs)

In order to select regions that were unbiased in their response patterns across condition, we ran an ANOVA of event type (clear/correct, clear/errors, and ambiguous) × timecourse (8 frames). The interaction of event type and timecourse image identified voxels in which activity related to these three event types differed over time. Importantly, the relationship of the activity for the three event types was not required to be in any particular direction in order for a region to be selected. In other words, some of the regions in this map could show correct > error or clear > ambiguous activity. It need not be that these regions show the pattern of activity we predicted (error > correct and/or ambiguous > clear). Functional ROI volumes were defined by growing regions around peak voxels using algorithms developed by Abraham Snyder (Wheeler et al., 2006). This procedure resulted in 9 ROIs (see Table 1). To examine the directionality of the effects driving the interaction, we then submitted these ROIs to further testing in a repeated measures ANOVA of event type (clear/correct, clear/errors, ambiguous) × timecourse (8 frames) using stepwise regressors of reaction time and response consensus.

Table 1
The list of regions of interest defined from the event type (clear/correct, clear/errors, and ambiguous) × timecourse (8 frames) repeated measures ANOVA. x, y, and z values correspond to stereotactic coordinates in MNI space. dACC/msFC: dorsal anterior cingulate cortex/medial superior frontal cortex; aI/fO: anterior insula/frontal operculum; dlPFC: dorsolateral prefrontal cortex.

ROI	Coordinates			Corrected statistics
	x	y	z	Z (all p's < .001)
dACC/msFC (dorsal)	−2	19	49	15.28
Left aI/fO (medial)	−33	24	1	15.65
dACC/msFC (ventral)	−2	28	37	14.39
Right aI/fO (medial)	33	25	−1	13.50
Right aI/fO (lateral)	45	23	−4	12.92
Left dlPFC (posterior)	−45	8	33	12.27
Left dlPFC (anterior)	−47	25	28	11.54
Left aI/fO (lateral)	−51	18	13	12.31
Left subcortical	−10	−12	11	8.45

Results

Behavioral

Reaction time

A task (semantic, phonological) × condition (ambiguous, clear/correct, errors) repeated measures ANOVA revealed a significant main effect of task ($F_{(1,35)} = 6.66$, $p = .01$), and pairwise comparisons (LSD corrected) revealed that RTs were longer for the phonological task than the semantic task (mean RT ± standard error: S = 1400.5 ± 21.7, P = 1470.5 ± 31.7). There was also a significant main effect of condition ($F_{(2,34)} = 160.75$, $p < .001$), such that RTs were longer for ambiguous and error trials, as compared to clear trials (p's < .001), but there was no significant difference between ambiguous and error trials ($p = .28$; mean RT ± standard error: ambiguous = 1510.5 ± 24.4, errors = 1490.2 ± 28.7, clear = 1305.8 ± 23.8). Finally, there was a significant task × condition interaction ($F_{(2,34)} = 57.33$, $p < .001$), such that, for both errors and clear trials, RTs were longer for the phonological task than the semantic task ($p = .047$, $p < .001$, respectively), but there was no difference in task for RTs on ambiguous trials ($p = .78$; Fig. 3a).

Accuracy/response consensus

To examine accuracy, we included only the clear trials, as there was no correct response defined for the ambiguous items. A paired samples t-test revealed that participants were significantly more accurate on the semantic task than on the phonological task ($t(36) = 4.728$, $p < .001$; mean accuracy ± standard error: S = 95.7 ± 0.4, P = 92.8 ± 0.6). Finally, there were individual differences (i.e., variance) in ratings of ambiguous stimuli (Fig. 3b), as seen in previous work (see Neta et al., 2009).
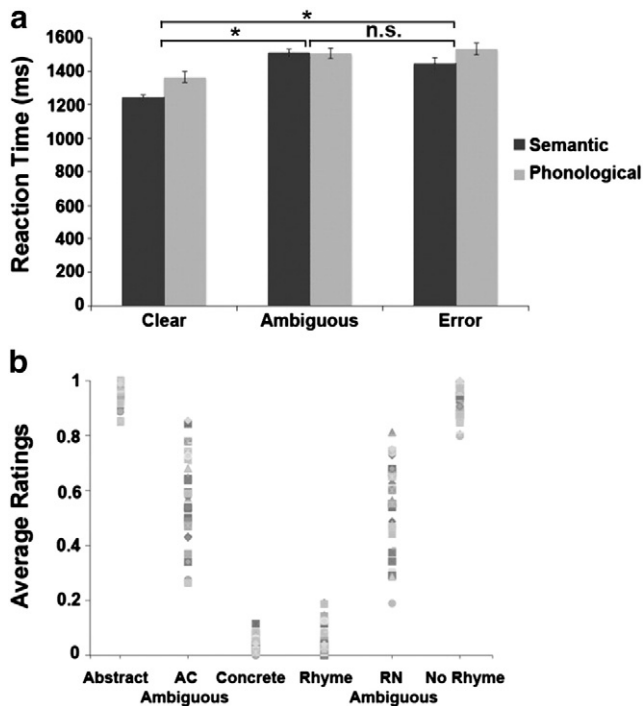

Fig. 3. The behavioral results. (a) Reaction time. RTs were longer for the phonological task than the semantic task, and they were longer for ambiguous and error trials, as compared to clear trials, but there was no significant difference between ambiguous and error trials. (b) Ratings. Clear stimuli had a higher response consensus than ambiguous stimuli. Also, there were individual differences (i.e., variance) in ratings of ambiguous stimuli, as seen in previous work (see Neta et al., 2009).

Imaging

Cingulo-opercular regions are modulated by each of the three signals

We first modeled the response to our three effects of interest (reaction time, response consensus, and errors) by including the first two as stepwise regressors in a voxelwise whole-brain repeated measures ANOVA of event type (errors, ambiguous, clear) and timecourse (8 frames). Fig. 4a shows a whole-brain map of regions that are modulated by reaction time (as modeled by the reaction time regressor). Fig. 4b shows a map of regions that are additionally modulated by response consensus (as modeled by the response consensus regressor), after the reaction time effects have been regressed out (i.e., effects of response consensus above and beyond the effects of reaction time). Fig. 4c shows a map of regions that are modulated by errors (from the interaction of error events × time within the omnibus event type × time ANOVA), after both reaction time and response consensus have been regressed out (i.e., additional effect of errors, above and beyond the other two effects). Finally, Fig. 4d shows the summation of Fig. 4a–c, identifying regions that are modulated by each of the three effects (reaction time, response consensus, and errors; i.e., a sum of Fig. 4a–c; for a list of coordinates, see Inline Supplementary Table S2). This figure shows the regions that are modulated by each effect independently, as well as those regions that are modulated by any combination of the three effects. As can be seen in Fig. 4d, there was a convergence of the three responses (reaction time, ambiguity, and errors) in the cingulo-opercular regions.

Inline Supplementary Table S2 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

To investigate the generalizability of these effects to other control networks, we examined 7 previously defined cingulo-opercular regions and 11 previously defined frontoparietal regions (Dosenbach et al., 2007). We found that the pattern of results that suggested separable processes was consistent in 5 of the 7 cingulo-opercular regions (not including the bilateral anterior prefrontal ROIs), but that this pattern was identified in only 2 of the 11 frontoparietal regions (only in bilateral dlPFC; Inline Supplementary Fig. S5).

Brain regions exhibiting an interaction of event type and time

In a voxelwise whole-brain repeated measures ANOVA with the factors of event type (errors, ambiguous, clear) and timecourse (8 frames), we found an interaction of event type and timecourse in, among other regions, the dACC/msFC (−2, 19, 49) and bilateral aI/fO (right aI/fO: 33, 25, −1; left aI/fO: −33, 24, 1; Fig. 5a). To explore the nature of the interaction, these regions were examined further using ROI analyses. Three of the top 4 ROIs were derived from the ANOVA map for event type activity (Fig. 5a), and the responses were averaged over the voxels within these regions. The cingulo-opercular regions showed a greater response to errors than ambiguous trials, which showed a greater response than clear trials, in all three regions (Fig. 5b). There was no main effect of task, but we have included timecourses for these responses separated by task (see Inline Supplementary Fig. S1). The results are qualitatively similar in both tasks as would be expected.

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

Stepwise regression supports three separable processes

When we regress out reaction time, the same effect is observed (i.e., errors > ambiguous > clear trials; Fig. 5c), but ambiguous trials are more differentiated from errors, as evidenced by a significant effect observed in dACC (errors > ambiguous). When we add the response consensus regressor (where response consensus is a percentage measure of agreement across participants for each stimulus, which we used as a proxy for ambiguity), the differences between ambiguous and clear trials are quantitatively eliminated (as expected in response to regressing out variance in ambiguity), but the error-related differences remain essentially intact (Fig. 5d). The effects reported here are
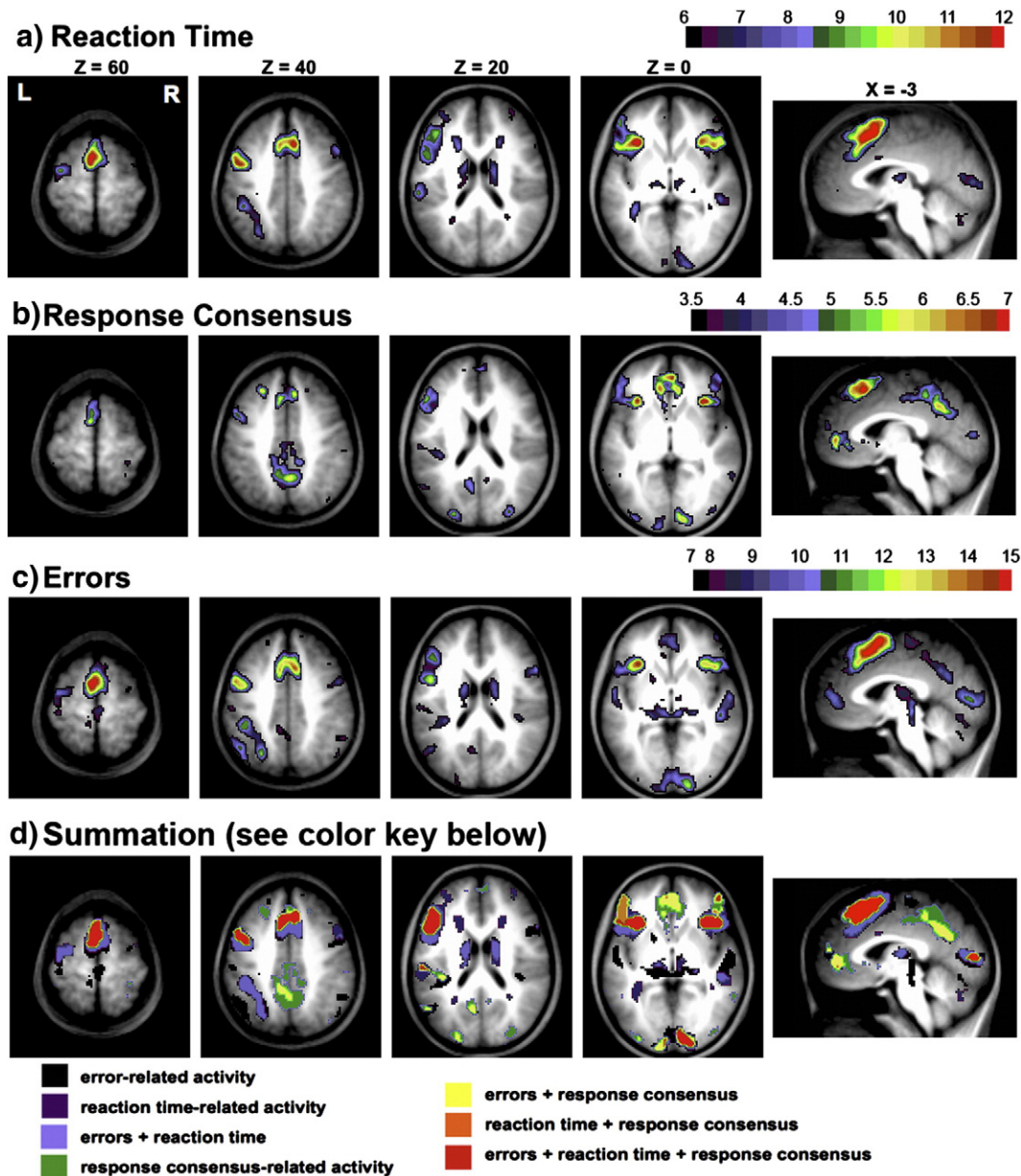
Fig. 4. Whole-brain results showing regions that are modulated by (a) reaction time, (b) any additional effect of response consensus, and (c) any additional effect attributable to errors. The thresholding for each image (*z* value) is shown above each map. (d) A summation map of regions that are modulated by all three effects (reaction time, response consensus, and errors; see the color key below this map).

similar when we ran the same stepwise regression using a scaled reaction time regressor (see Methods, Inline Supplementary Fig. S2). We find further support for this observation using regions derived from a previous report (Dosenbach et al., 2007), where the bilateral aI/fO and dACC/msFC (the first 3 regions—top left—in Inline Supplementary Fig. S5) show qualitatively similar results as do the regions identified using an ANOVA of the present data (Fig. 5).

Inline Supplementary Fig. S2 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

Effect of reaction time after equating ambiguity, and effect of ambiguity after equating reaction time

Because reaction time has some collinearity with ambiguity (average reaction time was significantly correlated with response consensus, but at $r = .26$, explaining only ~7% of the variance), we ran another analysis on the correct trials where we equated ambiguity. In other

words, we divided the trials based on a median split for reaction time, for the ambiguous and clear trials separately, but excluded trials in each condition in order to equate response consensus for ambiguous fast and slow trials ($p = .96$), and for clear fast and slow trials ($p = .39$, Inline Supplementary Fig. S3a). An average of 57 ambiguous trials, and 141 clear trials were included for each subject. An event type (clear/correct, ambiguous) × reaction time (fast, slow) ANOVA revealed that the cingulo-opercular regions showed a main effect of event type, and a main effect of reaction time, but no event type × reaction time interaction. We analyzed the same three ROIs (see Fig. 5), and found that activity was greater for slow than fast trials, in the ambiguous and clear conditions separately (Inline Supplementary Fig. S3b). See Supplemental Material, and Inline Supplementary Fig. S4, for another analysis of ambiguous and clear trials where we equated reaction time.

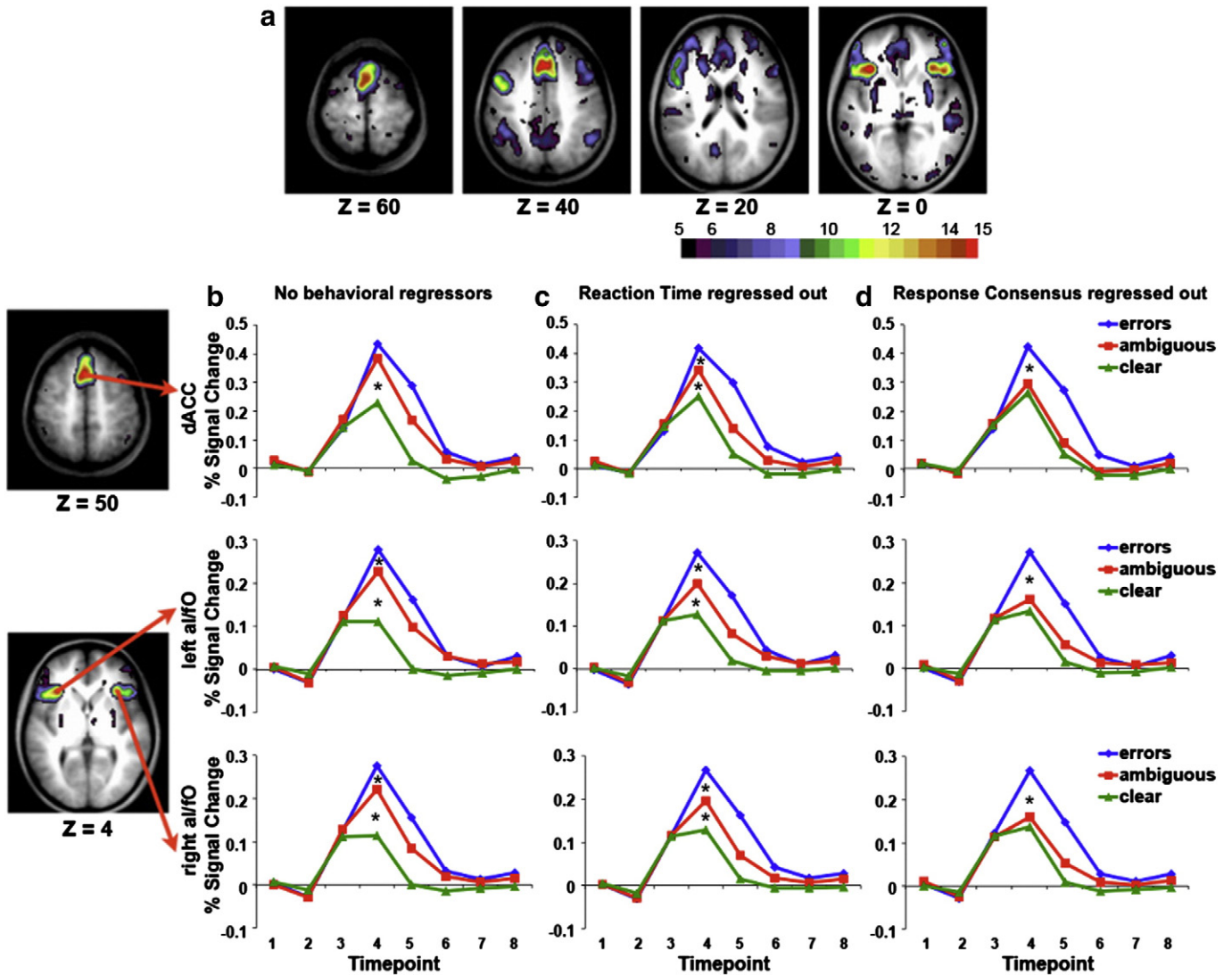Inline Supplementary Figs. S3 and S4 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

Fig. 5. (a) Whole-brain regions that showed a significant timecourse modulated by event type (clear, ambiguous, error trials). (b–d) Timecourses for regions of interest in three cingulo-opercular regions (dorsal anterior cingulate/medial superior frontal cortex and bilateral anterior insula/frontal operculum). (b) All regions showed a greater response to errors and ambiguous trials than clear trials. (c) When we regress out reaction time, the same effect is observed (i.e., errors > ambiguous > clear trials). (d) When we add a regressor for response consensus (where response consensus is a percentage measure of agreement across participants for each stimulus, which we used as a proxy for ambiguity), the differences between ambiguous and clear trials are quantitatively eliminated, but the error-related differences remain intact.

Discussion

The data in the present report suggest at least three separable effects at the trial level within cingulo-opercular regions: responses that are modulated by reaction time (i.e., time on task), those that are modulated by response consensus (i.e., ambiguity), and those that are modulated by accuracy (i.e., errors). Importantly, regressing out reaction time does not delete the effect of ambiguity (response consensus) in cingulo-opercular regions, and regressing out both reaction time and response consensus diminishes the ambiguity-related, but not error-related, signals. As such, the error-related effects remain intact even after the other two effects are regressed out. Moreover, we demonstrated that there are reaction time effects in these regions even when controlling for errors and ambiguity. If these effects were all driven by a single process that accumulated activity with processing time, (e.g., task difficulty), then regressing out reaction time (one measure thought to reflect task difficulty), would minimize the differences among the error and ambiguity signals. However, when we regressed out reaction time, the same effect is observed (i.e., errors > ambiguous > clear/correct trials; Fig. 5c). Another possibility is there is some other third

variable that represents a single process that is associated with each of these three effects. For example, it could be that error and ambiguity signals relate to some generic uncertainty processing. If some third variable could explain all of the effects, then regressing out ambiguity should reduce not only the ambiguity signal, but also have some consequence on the error signal. However, regressing out response consensus (our proxy for ambiguity), quantitatively eliminated the ambiguity signal, but left the error signals essentially intact (Fig. 5d).

This combination of results strongly suggests that there is not a single process that can explain these different responses. Rather, there appear to be multiple forms of performance feedback that are separately computed or reported to cingulo-opercular regions (at least in the case of dACC/msFC and aI/fO). The trial-related effects can be seen as separate feedback signals useful for control adjustment across trials or task blocks. Fig. 6 presents an extended model of cingulo-opercular task control, originally proposed in Dosenbach et al. (2007), suggesting that several types of performance feedback signals, including errors, ambiguity/conflict, and reaction time, can be computed in the cingulo-opercular regions at once. Thus, we propose that the cingulo-opercular system can accept or compute, and presumably utilize, many forms of
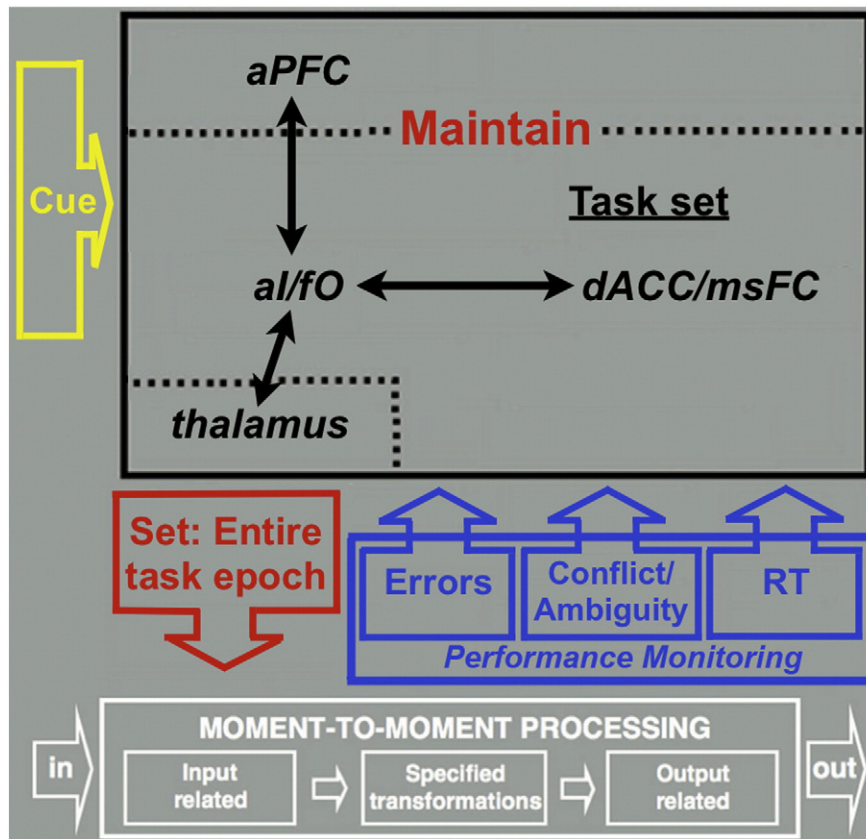
Fig. 6. A revised model of cingulo-opercular task control, originally proposed in Dosenbach et al. (2007). The cingulo-opercular network interprets cues, affects downstream processing in a more stable fashion, as well as implements top-down control, and processes bottom-up feedback. Importantly, the present work extends these findings by also suggesting that several types of performance feedback signals can be computed or utilized in the cingulo-opercular regions at once, including errors, ambiguity/conflict, and reaction time.

performance feedback in the service of providing more effective top-down signals in later trials, or later epochs, or for the performance of similar tasks in the future.

Importantly, there are other networks (e.g., frontoparietal) that have been implicated in task control. Our preliminary examination of these signals in the frontoparietal regions showed that only the dlPFC supports these separable processes (see Inline Supplementary Fig. S5 for a comparison of responses in 7 cingulo-opercular and 11 frontoparietal timecourses). The purpose of the current study was to outline the role of cingulo-opercular regions in performance-related signals, and perhaps future work can more specifically target the nature of these signals in dlPFC, as well as examine the role of the frontoparietal network in supporting these signals, more generally. However, we mention, briefly, that previous work has shown that one strong dividing line between frontoparietal and cingulo-opercular control signals is their timing within an extended trial. Frontoparietal differences between error and correct trials begin early in the trial (during evidence accumulation), while cingulo-opercular regions withhold activity to the time of decision (much more fitting a feedback idea; Ploran et al., 2007). Moreover, consistent with the model proposed by Dosenbach et al. (2007), our current best bet is that the frontoparietal network is more important for short-term or adaptive control/adjustment, and the cingulo-opercular network is more important for stable control.

Inline Supplementary Fig. S5 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

Interestingly, previous work has used an approach similar to the present report in order to demonstrate that the anterior cingulate value signal, which has previously been dismissed as simply a consequence of response competition, remained after regressing out reaction time, and after dividing the trials into different trial types (Kolling et al.,

2012). In contrast, other work has shown that when reaction time is accounted for, some of the processing distinctions in the cingulate (e.g., error, conflict) appear minimal or absent (Grinband et al., 2011). This work argues that the cingulate region is associated with a process primarily modulated by reaction time (e.g., sustained attention, effort, working memory), with slower reaction times (i.e., more time on task) eliciting greater activity. However, Grinband et al. (2011) performed specific contrasts where RT was binned into conditions (e.g., slow congruent, fast incongruent), and binned into quantiles for each voxel, which effectively gives equal weight (1/10th) to each RT quantile when comparing the BOLD response between conditions. Our approach takes a closer look at specific ROIs before and after regressing out RT (not dependent on threshold, and not by binning RT into conditions). We frankly would have expected the Grinband study to show separable effects, but perhaps the categorical nature of the Stroop manipulation changed the situation enough that they became more collinear.

More recently, another similar approach has shown that a simple reaction time task shows overlapping effects with congruency effects (incongruent > congruent activity in a Stroop task), suggesting that a reaction time account for these congruency effects may be more valid than a conflict monitoring account (Weissman and Carp, 2013). Specifically, Weissman and Carp (2013) used a response-interference task and a simple RT task and showed that there is an overlap in the maps derived from RT in both tasks and from the congruency effect in the interference task. They suggest that, because ACC showed the effects of RT in both tasks (and did not differ between tasks), this is consistent with the time on task account for ACC, but not with the conflict monitoring account. We would argue that they show evidence for RT effects in both tasks, but also the effects of congruency, and that the ACC shows

both types of effects, instead of trying to use RT effects to explain conflict effects. In other words, their results are not inconsistent with those reported here, and perhaps our ability to linearize "conflict"/ambiguity allowed us to separate it more clearly within a task.

Indeed, the idea that a single cortical region can be responsible for multiple information processes is not a novel concept. For example, the knowledge that the posteriormost aspect of the cerebral cortex is related to vision extends back more than a century to the work of Inouye and Holmes (Holmes and Lister, 1916; Inouye, 1909). Having an end-point that would characterize the contribution of primary visual cortex to the general category of "doing vision" neglects the broad knowledge we have accumulated in the intervening century about this region. Among many other things, it is commonly held that primary visual cortex is composed of distinct processing modules that include blobs more associated with color processing (see Blasdel, 1992), a layer (layer 4B) related more to high frequency visual information (including direction selectivity), and horizontally arranged pinwheels relating to orientation selectivity (see Kandel, 2000; Wurtz and Kandel, 2000). These anatomically separate processing "modules" also have differential projections to downstream regions.

It is difficult, then, to imagine a debate between vision neuroscientists arguing whether, for example, primary visual cortex is a color-processing region or whether it instead processes visual motion. The reality is that primary visual cortex, in fact, contributes, at least somewhat separately, to the processing of both kinds of visual information. Yet, this sort of debate is common in cognitive neuroscience where there are often attempts to come up with a single process explanation for a particular piece of cortex (or other brain region).

Here, we suggest that, similar to V1 relating to vision (i.e., a thematic level of interpretation), the major contributions of the cingulo-opercular regions may relate to a theme of "task control". Indeed, these regions have been implicated in many domains of control and regulation, including motor control (Ackermann and Riecker, 2004; Paus, 2001), self-regulation (Heatherton, 2011; Wagner and Heatherton, 2010), thought suppression (Mitchell et al., 2007), and emotion regulation (Ochsner et al., 2012; Wager et al., 2008). Given the important observations that these regions also produce other signals important for task control (task initiation, and task maintenance, see Introduction; Fig. 6), we propose that the trial-related signals examined here represent separate performance feedback signals that are crucial for task control, broadly. Specifically, we have shown that there are at least three such performance feedback signals that relate to reaction time, ambiguity, and accuracy of a given trial. We propose that the different activations reported here index multiple forms of feedback, which would then entail different forms of adjustment of control in order to improve future performance. In other words, just as V1 subserves multiple separable visual processes, the regions of the cingulo-opercular network contain multiple feedback processes, along with other control-related signals. Taken together, the trial-related effects in turn can be seen as separate feedback signals useful for control adjustment across trials or task blocks.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.053.

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