Task Context and Frontal Lobe Activation in the Stroop Task

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Short title: Task Context and the Anterior Cingulate

Keywords: fMRI, cueing effects, congruency effect, partial least squares analysis

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ABSTRACT

The ability to step outside a routine – to select a new response over a habitual one – is a cardinal function of the frontal lobes. A large body of neuroimaging work now exists pointing to increased activation within the anterior cingulate when stimuli evoke competing responses (incongruent trials) relative to when responses converge (congruent trials). However, lesion evidence that the anterior cingulate cortex (ACC) is necessary in this situation is inconsistent. We hypothesized that this may be a consequence of different task procedures (context) employed in lesion and neuroimaging studies. The present study attempted to reconcile the lesion and fMRI findings by having subjects perform clinical and experimental versions of the Stroop task during BOLD fMRI acquisition. We examined the relationship of brain activation patterns, specifically within the anterior cingulate and left dorsolateral frontal regions, to congruent and incongruent trial types in different task presentations or contexts. The results confirmed our hypothesis that ACC activity is relatively specific to unblocked uncued incongruent Stroop conditions that have not been employed in large neuropsychological studies. Moreover, the size of the behavioral Stroop interference effect was significantly correlated with activity in the ACC and left dorsolateral regions, although in different directions. The current results are discussed in terms of previous proposals for the functional roles of these regions in activating, monitoring, and task setting and the relation of these findings to the disparate reports in recent case series is considered.

INTRODUCTION

The neural basis of cognitive control is a crucial piece of information in any biological account of complex behavior and has rightfully garnered significant attention in cognitive neuroscience. Many studies of cognitive control employ cognitive paradigms, such as the Stroop task (Stroop, 1935), that pit automatic response tendencies against more controlled ones. In the Stroop task, subjects are required to name the font colour of colour words as quickly and accurately as possible. The font colour and word can be congruent (‘red” written in red) or incongruent (“red” written in blue). Response times (RTs) are generally longer for incongruent stimuli and the ‘interference effect, or RT difference between these stimulus types, is generally thought to reflect the process of overcoming the conflict created by the more automatic response tendency (reading the word).

A large body of functional Magnetic Resonance Imaging (fMRI) data indicates that the anterior cingulate cortex (ACC) is consistently involved in these situations and recent work has attempted to further define the cognitive processes associated with ACC activation. Several candidate functions have been proposed for the ACC based on Stroop tasks and similar paradigms. Some theoretical perspectives favour an evaluative role in detecting conflict between stimuli or responses (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 2000; Milham et al., 2001; Zysset et al., 2001) or monitoring performance for errors (Garavan, Ross, Murphy, Roche, & Stein, 2002; W. J. Gehring & Knight, 2000), whereas others have argued for a more active role in instantiating control of attention or activation (Alexander & Stuss, 2006; Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Ochsner et al., 2004; Paus, 2001; Paus, Petrides, Evans, & Meyer, 1993; Shallice, Stuss, Alexander, Picton, & Derkzen, 2008; Stuss et

al., 2005). Yet, despite the vast amount of data and theoretical discussion, the *necessary* role of the ACC in performance of the Stroop task has not yet been established.

Converging evidence from studies of patients with lesions to the anterior cingulate is required to confirm that the ACC is necessary in these situations and would help to disentangle the precise role of ACC in this context. Unfortunately, consistent evidence has not been forthcoming. In the first neuropsychological study of Stroop performance in 118 patients with focal lesions, Perret (1974) found that Stroop performance was impaired in patients with lesions to the left dorsolateral prefrontal region. Vendrell and colleagues (Vendrell et al., 1995) later studied Stroop performance in 32 focal lesion patients and reported that impairment was associated with right lateral prefrontal lesions. Most recently, we evaluated 51 patients with focal lesions and found poor Stroop performance after left dorsolateral lesions (Stuss, Floden, Alexander, Levine, & Katz, 2001). Since the left dorsolateral lesions also caused impairment in the colour naming condition, the necessary relationship with the left lateral region was unclear. Moreover, we also found that superior medial lesions, particularly involving the right supplementary motor area, were associated with errors during the interference condition of the Stroop task. We proposed on the basis of this and other findings (Alexander et al., 2007; Stuss, Shallice, Alexander, & Picton, 1995) that, in a blocked interference condition, superior medial regions of the frontal lobes are involved in an energization process whereby relevant response schemas are endogenously maintained in an activated state. It was feasible that a relationship between ACC lesions and Stroop performance was simply obscured by grouping patients with heterogeneous superior medial lesions, so we looked specifically at patients with lesions that involved the ACC. However, post-hoc analysis failed to identify any association.

The lack of concordance between our group study and the growing body of fMRI literature describing prominent ACC activations during similar tasks was puzzling. In that paper, we proposed that the discrepancy might arise from the fact that the task context in our, and other, neuropsychological studies was different from that in most fMRI experiments. Namely, patient studies have mostly employed standardized versions of the Stroop task, involving repeated presentation of homogeneous trial types in a blocked format (i.e., 100 color naming trials followed by 100 incongruent trials). In contrast, task design used in functional neuroimaging studies has tended to involve stimulus runs that mix trial types (i.e., incongruent and congruent trials). As others have pointed out before (Gratton, Coles, & Donchin, 1992; Kerns et al., 2004), the context in which an incongruent stimulus is presented has implications for the cognitive processes necessary to respond accurately. ACC participation could also be dependent on the task context. Similar inconsistencies in lesion and activation loci have been noted in comparisons of clinical and experimental versions of other neuropsychological measures. For example, Stuss and colleagues (Stuss, Bisschop et al., 2001) found that impaired performance on Part B of the clinical version of the Trail Making Test was related to dorsolateral lesions. Functional MRI studies of Trails B report activations in the left lateral frontal areas but the relevance of ventral versus dorsal regions appears to depend on task design (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Zakzanis, Mraz, & Graham, 2005).

There are several small series or case studies in patients with more or less selective lesions of the ACC that use the mixed trial type Stroop procedure employed in fMRI studies. While an association between ACC lesions and performance is observed, the results are still far from consistent. For example, Fellows and Farah (2005) studied four patients with lesions to the anterior cingulate and found intact performance on two versions of the Stroop task that involved

mixed trial types. Turken and Swick (1999) had also reported a patient with a right ACC lesion who also showed intact performance on a variant of the Stroop despite mixed trial types. Other case studies and case series have yielded opposite findings. Swick and Turken (2002) and Swick and Jovanovic (2002) reported another patient who showed impaired performance in a variety of procedures. Likewise, Ochsner and colleagues (2001) reported a patient who showed intact Stroop performance prior to bilateral cingulotomy and impaired performance after the procedure. More recently, a case series of 8 patients with anterior communicating artery aneurysm lesions restricted to ventral medial frontal lobe and rostral anterior cingulate cortex revealed slowed responses to incongruent stimuli on a spatial compatibility Simon task, but only when incongruent trials followed congruent trials (di Pellegrino, Ciaramelli, & Ladavas, 2007). It should be noted, however, that the nature of cognitive conflict differs depending on the task stimuli (Egner, 2008) and therefore it may be inappropriate to equate findings across investigations that employ different stimuli.

The goal of the present study was to use fMRI to test our original hypothesis that task context, by which we mean the stimulus conditions under which trial types occur, could account for the conflicting findings regarding the relevance of ACC in performance of the Stroop task. We directly compared the blocked trial type Stroop procedure used in our group study with a mixed trial type version (both with and without stimulus cues). In the blocked context, trial types were identical within a run and the upcoming trial type (e.g., congruent or incongruent) was fully predictable. Self-initiated maintenance of the relevant task set/responses could be used to maximize performance. In the unblocked uncued context, trial types were interleaved and the upcoming trial type was completely unpredictable. Therefore, task set/responses were switched or activated only by the appearance of the stimulus and it was not possible to engage preemptive

processing to maximize performance. Finally, in the unblocked cued context, trial types were interleaved but preceded by an informative cue that signaled the upcoming trial type. This provided an external impulse to switch or activate the relevant task set/responses in advance of the stimulus to maximize performance. We predicted that anterior cingulate activation would be prominent on incongruent trials only in the context of mixed (unblocked) stimulus-types. Moreover, we predicted that a stimulus cue to externally trigger the non-routine task set would also minimize the contribution of ACC.

As a corollary, we were interested in the influence that task context had on left dorsolateral activation. A growing literature suggests that this region plays an important role in task setting or in setting the criteria for a response (MacDonald, Cohen, Stenger, & Carter, 2000; Stuss, Binns, Murphy, & Alexander, 2002; Vallesi, McIntosh, Alexander, & Stuss, 2009). We hypothesized that left dorsolateral prefrontal regions would be prominent in contexts where the task could be anticipated or set in advance and that greater activations of this region would be associated with better cognitive control. Finally, we were interested in observing how task context might moderate the relation between ACC and left dorsolateral prefrontal cortex. Given the hypothesized role of the superior medial region in an energization process and the left dorsolateral region in task-setting processing, either of these processes would come into play during performance on the Stroop task, although they would be expected to have complementary roles. As such, we predicted that ACC and left dorsolateral activity would show inverse relations, such that greater activity in one area would be associated with attenuated activity in the other.

As an initial, unbiased step, we used a multivariate analysis approach, Partial Least Squares (PLS) (McIntosh, Bookstein, Haxby, & Grady, 1996), to increase the sensitivity of our

analysis to detect distributed patterns of brain activity involved in the Stroop task (McIntosh, Chau, & Protzner, 2004; Vallesi et al., 2009). Specifically, the Task-PLS identifies cohesive patterns of brain activity that co-vary with the experimental conditions in different task contexts, thus emphasizing the principle that the brain works through dynamic and integrated network interactions and not by means of isolated voxel activations (see McIntosh, 2000 for a full consideration of this issue). Given our a priori hypotheses, we subsequently correlated activations in the prefrontal areas extracted by the PLS analysis with the magnitude of the Stroop effect.

METHODS

Subjects

Nine right-handed, neurologically-normal, young adults (5 males; mean age = 27.8, SD=4.0, range 21-33; mean years of education = 19.3, SD = 3.3, range 16-25) received $50 for participating in the study. All had normal or corrected-to-normal vision and had no history of neurological or psychological disorder. The study was approved by the Baycrest Ethics Review Board and all subjects provided informed consent to participate.

Task

The task consisted of four trial types. On word reading trials, the word RED, GREEN, or BLUE appeared in black print and the subject was required to press one of three buttons in response to the meaning of the word. On neutral colour naming trials, a string of three, four, or five Xs appeared in either red, green, or blue print and the subject was to indicate the colour of the Xs via a button press. On congruent and incongruent trials, the word RED, GREEN, or BLUE appeared in coloured print which either corresponded (congruent) or conflicted (incongruent) with the meaning of the word (e.g., RED in red print or RED in blue print,

respectively). In both these trial types, the subject was to press a button in response to the colour that the word was printed in rather than its meaning. Responses and response time (RT) were recorded on a pair of Lumitouch (Photon Control, Inc.) paddles with the middle (red) and index (green) fingers of the left hand and the index (blue) finger of the right hand.

The task stimuli were back-projected onto a screen positioned at the entrance of the bore and subjects viewed the stimuli via a mirror mounted to the head coil. All stimuli were presented centrally against a white background. Each trial began with a black cue for 500 ms which was replaced by a blank screen for 1500 ms. A target stimulus then appeared for 2000 ms and was replaced by a blank screen for a variable interval (8 to 14 seconds). The task was presented under three presentation conditions or contexts: blocked (a group of identical trial types), unblocked-uncued (psuedorandomized trial types), and unblocked-cued (psuedorandomized trial types preceded by meaningful cues). In the blocked-uncued and unblocked-uncued contexts, the cue ('+++') did not provide any information about the upcoming target stimulus. In the unblocked-cued context, the cue provided information about the upcoming trial type. Subjects were instructed that a 'WRD' cue signaled a word reading trial, a 'XXX' cue signaled a neutral colour naming trial, and a 'CLR' cue signaled a congruent or incongruent colour naming trial. The same cue was employed for both congruent and incongruent trials to encourage similar pre-stimulus cognitive strategies for these two trial types.

The task was presented in a consistent order for all subjects, with 20 trials in each of 12 runs. Runs one through four involved blocked-uncued presentation of word reading, neutral colour naming, congruent, and incongruent trials, respectively. Subjects received task instructions for the relevant trial type at the beginning of the run. Neutral colour naming run occurred prior to the congruent and incongruent runs to ensure equal practice with stimulus-

response mapping. Blocked runs occurred early to ensure that all subjects were equally experienced with trial type instructions at later runs. Runs 5, 7, 9, and 11 involved unblocked-uncued presentation of 5 trials of all four trial types in pseudo-random order such that no more than two identical trial types could occur consecutively. At the beginning of each run, subjects were instructed that different trial types would be mixed together and that they should perform the task associated with each stimulus (i.e. read black words, name the colour of coloured X's, and name of the colour of a coloured word). Runs 6, 8, 10, and 12 involved unblocked-cued presentation of 5 trials of all four trial types in the same pseudo-random order. At the beginning of each run, subjects were again instructed that they would be seeing all of the different trial types mixed together but that this time they would receive a warning cue that would tell them what type of stimulus was about to appear and that they should use this cue to prepare for the stimulus. Cued and uncued unblocked runs were interleaved to ensure that no context was more influenced by fatigue over the course of the scanning.

Another consideration was the issue of stimulus frequency. In many studies of cognitive control in Stroop and other conflict-inducing tasks, stimulus frequency is confounded with control requirements such that the stimulus requiring the greatest control is also less frequent. In the current study, incongruent and congruent trials occurred in the context of additional neutral and word reading trials which allowed these stimuli to occur with the same low (25%) frequency. Thus, there were no differences in stimulus expectancy between congruent and incongruent trials. Moreover, the presence of simple word reading trials ensured that word reading remained a viable task option and prevented adoption of strategies (i.e., unfocusing one's eyes, narrowing the spatial extent of attention) that would reduce the interference aspect of the task. The current report was concerned primarily with the behavioural and activation patterns associated with the

congruent and incongruent trials, and the analysis and results are therefore restricted to these trial types.

fMRI scanning and data analysis

Blood oxygenation level-dependent (BOLD) images were acquired using a 1.5-T Signa MR scanner with a standard head coil (CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). Twenty-six 5 mm-thick axial slices were obtained using a single shot T2*-weighted pulse sequence with spiral readout, offline gridding, and reconstruction. Repetition Time (TR) = 2000 ms, TE = 40 ms, flip angle 80°, 90 × 90 effective acquisition matrix). Subjects underwent 12 scan sequences of approximately six minutes. Standard volumetric anatomical MRI was performed before functional scanning using a standard 3D T1-weighted pulse sequence (TR = 12.4 ms, TE = 5.4 ms, flip angle 35°, 22 × 16.5 field of view, 256 × 192 acquisition matrix, 124 axial slices 1.4 mm thick).

Data pre-processing was performed using Analysis of Functional NeuroImages software (AFNI version 2; (Cox & Cox, 1996; Cox & Hyde, 1997). The initial 30 seconds of each run were excluded to allow scanner stabilization. The remaining time-series data were spatially co-registered to correct for head motion using a 3D Fourier transform interpolation. Twelve event types were selected based on trial type and context: word reading, neutral colour naming, congruent colour naming, and incongruent colour naming for each of the blocked-uncued, unblocked-uncued, and unblocked-cued contexts. Only correct congruent and incongruent trials were included in the analysis, and mean activations were regressed from the functional data. Activation images were then transformed into stereotaxic space (Cox & Cox, 1996; Cox & Hyde, 1997; Talairach & Tourneaux, 1988) and spatially smoothed with a Gaussian filter with FWHM

6 mm full width at half maximum (FWHM) to account for individual variation of the anatomical landmarks to facilitate the subsequent group analysis.

Task-PLS analysis

PLS carries out the computation of the optimal least squares fit to cross-block correlation between the independent and dependent measures. In PLS independent measures are the experimental manipulations, behaviour or activity of a seed region, while the dependent measures are represented by the pattern of activations/deactivations in the whole brain (McIntosh et al., 1996; McIntosh & Lobaugh, 2004). PLS is particularly sensitive in detecting distributed patterns of brain activity (McIntosh et al., 2004). In particular, task-PLS identifies patterns of brain activity that co-vary with the experimental conditions. In other words, the Task-PLS analysis permits identification of activation patterns that maximally differentiate between task conditions in an atheoretical manner. Note that this reflects brain activity in the state of performing a particular condition, rather than the actual performance measure (i.e., RT would be used in a Behavior-PLS analysis). Six task conditions (2 trial types: congruent vs. Incongruent; x 3 contexts: Blocked, Cued, Uncued) were included in this analysis. For each condition, the haemodynamic response function (HRF) of each voxel was defined as the mean percent change in signal intensity during 7 consecutive post-stimulus TRs (2 sec each) relative to the baseline, which was defined as activity during the TR immediately prior to trial onset (lag 0). No assumption was made about the shape of HRF. The data matrix, containing all voxels and associated temporal segments (columns) for all conditions and subjects (rows), was mean-centered column-wise with respect to overall grand average. The matrix was decomposed using singular-value decomposition (SVD) to produce a set of mutually orthogonal latent variables (LVs) with decreasing magnitude. Each latent variable contained three kinds of information:

design scores (contrasts between experimental conditions); a singular image (shows how the spatio-temporal distribution across the brain relates to the identified contrasts); and a singular value (expresses the strength of the relationship between design scores and the singular image). Therefore, a LV represents how spatiotemporal pattern of brain activations co-vary with the experimental conditions.

The significance for each LV as a whole is determined using a permutation test (Edgington, 1986). The data matrix rows are randomly reordered and a new set of LVs is calculated at each permutation. The singular value of each new LV is compared to the singular value of the original LV. A probability is assigned to the initial value based on the number of times a statistic from the permuted data exceeds this original value. For the current experiment, 1000 permutations were used. If the probability was less than 0.05 then the LV was considered significant.

Voxel saliences are weights that indicate how strongly a given voxel contributes to a LV. To determine the reliability of the saliences for the voxels characterizing each pattern identified by the LVs, all data were submitted to a bootstrap estimation of the standard errors, by randomly re-sampling subjects with replacement 200 times. PLS is recalculated for each bootstrap sample to identify those saliences whose value remains stable regardless of the sample chosen (Sampson, Streissguth, Barr, & Bookstein, 1989). The ratio of the salience to the bootstrap standard error (bootstrap ratio, BSR) is approximately equivalent to a z score (Efron & Tibshirani, 1986). For each lag, clusters with at least 10 contiguous voxels with a BSR ≥ 4 (approximately equivalent to a z-score corresponding to $p < .0001$) were considered as reliable and reported. Coordinates of the voxel with the peak BSR within each cluster were obtained in MNI space and converted into Talairach space to find the likely gyral locations using M. Brett's transformation

(http://www.mrccbu.cam.ac.uk/Umaging/mnispace.html). Approximate Brodmann areas were then identified using the Talairach Daemon tool (Lancaster et al., 2000).

To understand the relation between the polarity of the saliences in the singular image and the direction of HRF change in the areas reliably activated in each LV, it is useful to relate the saliences to the design scores. For instance, positive saliences would indicate voxels that are relatively more active in conditions with positive design scores.

Since the PLS analysis has not been used in the fMRI literature on the Stroop task, we also performed a standard GLM random effect analysis with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). To increase comparability between the two analyses, three aspects were kept constant. First, no assumption was made about the shape of the haemodynamic response and a finite-impulse-response (FIR) function was used with a total window length of 14 s and an order of 7. Such a model estimates the detected signal as response to the stimulus individually for each of the first 7 TRs after trial onset. Second, the optimal contrasts reflected in the PLS design scores of LV1 were used in the GLM analysis, since those addressed our a priori hypotheses concerning an effect of context in modulating brain activations underlying Stroop interference. Third, since the main effects of interest in the PLS analysis were obtained between TRs 2 and 6, the same contrast was applied to the TRs 2-6 considered together. To correct for multiple comparisons, we chose a standard family-wise error (FWE)-corrected threshold of $p < 0.05$ at the cluster level.

RESULTS

Behavioural measures

The experiment-wide error rate was very low (3.3%). There was no effect of condition or trial type on the number of errors (all p = n.s.). All behavioural and fMRI analyses involved only correct trials.

Figure 1 illustrates RTs in each condition for each trial type. There were significant main effects of context ($F(2,16) = 4.6$, $p < .05$) and trial type ($F(1,8) = 21.5$, $p < .01$), as well as a significant interaction ($F(2,16)= 7.9$, $p < .01$). Overall RTs were shorter in the unblocked cued context relative to the unblocked uncued context, indicating that subjects were able to use the trial-type cues to prepare for an upcoming stimulus. Planned comparisons indicated that the Stroop effect (incongruent RT – congruent RT) in the Unblocked Uncued context (203ms) was larger than in the Blocked context (96ms) ($t = 2.8$, $p < .05$; $d = .88$). The size of the Stroop effect in the Unblocked Cued context (144ms) did not differ from other contexts ($p>.05$).

(Insert Figure 1 about here)

Task-PLS Results

This analysis identified a significant spatiotemporal pattern of brain activations (Latent Variable 1, explained cross-block variance = 26 %, observed singular value: 43.6, $p < .001$) that differentiated between incongruent trials in the unblocked uncued context (and to a smaller degree, incongruent trials in the unblocked cued context; positive design scores and bootstrap ratios) and all the other experimental conditions. The design scores for this LV are shown in Figure 2. Reliable clusters with negative and positive saliences for the LV (bootstrap ratios $\geq \pm 4$, cluster size ≥ 10 voxels) are listed in Table 1 and illustrated in Figure 3.

(Insert Figures 2 & 3 about here.)

(Insert Table 1 about here.)

To better understand which contrast between experimental conditions was statistically significant, we submitted the brain scores (which reflect each subject's contribution to the design scores, and to the LV in general) to a 3x2 repeated measures ANOVA with context (blocked, unblocked uncued, unblocked cued) and congruency (congruent vs. incongruent) as the repeated measures factors. There was a main effect of context [$F(2, 16)=54.8$, $p < .00001$; unblocked contexts showed more positive brain scores than blocked] and of congruency type [$F(1, 8)=46.7$, $p=.001$; incongruent trial types had more positive brain scores than congruent ones]. More critically, these two factors showed a significant interaction [$F(2, 16)=16.4$, $p < .001$]. Consistent with our a priori hypothesis, a planned contrast ($t(8)=5.7$, $p<.001$) revealed that incongruent trials in the absence of a cue (unblocked uncued incongruent trials) showed greater engagement of the brain regions shown in Figure 3 than incongruent trials preceded by a cue (unblocked cued incongruent trials).

Critically, there was a reliable activation of clusters involving the right ACC and left dorsolateral prefrontal cortex (DLPFC), among others, and the associated haemodynamic response functions can be appreciated on Figure 4. The peak activation in the ACC cluster occurred in the anterior portion of the rostral cingulate zone (Picard & Strick, 2001) and is slightly more lateral and inferior than activation locations reported in many previous fMRI studies using a mixed trial design, although the cluster involves primarily ACC (BA 32).

(Insert Figure 4 about here.)

<u>Relation of Regional Activations to RT</u>

Right ACC (24,28,13): The right ACC activation difference between incongruent and congruent trials (average of lags 2 through 6) correlated positively with the size of the behavioural Stroop

effect in the Unblocked Uncued context ($r = .73$, $p > .05$), suggesting that subjects who showed larger Stroop effects also activated this area to a greater degree on incongruent trials (Figure 5, Panel A).

Left DLPFC (-55,29,28): The left DLPFC (BA 46) activation difference between incongruent and congruent trials (average of lags 2 through 6) correlated negatively with the size of the behavioural Stroop effect in the Unblocked Uncued context ($r = -.75$; $p < .05$), suggesting that subjects who showed smaller Stroop effects activated this area to a greater degree on incongruent trials (Figure 5, Panel B).

(Insert Figure 5 about here.)

Right ACC vs. left DLPFC: Differential activations in these regions correlated negatively with each other during the Unblocked Uncued context ($r = -.7$, $p < .05$), such that high ACC activations occurred in subjects who showed low DLPFC activations.

There were no significant correlations between Stroop effect and activations in either right DLPFC (51, 40, 16) or right (44,5,26) or left (-51,21,25) ventrolateral frontal cortex (all ps > 1). It should be noted that Task-PLS is blind to RT performance and therefore relations between brain activations and performance are immune to 'non-independence' criticisms (Vul, Harris, Winkielman, & Pashler, 2009).

SPM Results

Figure 6 depicts the clusters identified in the SPM analysis. As mentioned earlier, the SPM analysis employed the same contrast reflected in the PLS design scores of LV1 for lags 2 through 6 (as shown in Figure 2). SPM clusters included a large right medial cluster that extended to ACC and a cluster in the left DLPFC, although the Z-score peaks within those clusters were more superior and more posterior than in the PLS analysis, respectively. These results are

summarized in Table 2. This suggests that the distinct natures of the statistical analyses employed (multivariate in PLS vs. univariate in SPM) likely accounts for differences in peak locations (see McIntosh & Lobaugh 2004 for a full discussion on the likely sources of differences between SPM and PLS results).

(Insert Figure 6 about here.)

(Insert Table 2 about here.)

DISCUSSION

The goal of the current study was to begin to reconcile the disagreement between group lesion studies and neuroimaging findings, particularly with respect to the relevance of ACC and whether this brain region is 'necessary' for the ability to select the correct response in the presence of conflicting options. Our Task PLS analysis revealed a pattern of activated clusters (including the ACC) associated mostly with incongruent trials occurring in an unpredictable (unblocked and uncued) fashion. Incongruent trials presented in a blocked context, on the other hand, were not associated with this pattern of activation. The fact that ACC activation occurred primarily in this context supports our hypothesis that the mismatch between lesion and imaging findings is related to procedural differences. It makes intuitive sense that task context can fundamentally alter the processing requirements and thereby dictate which brain regions are necessary for performance (Burgund, Lugar, Schlaggar, & Petersen, 2005; Mostofsky et al., 2003).

An additional factor that differs between most lesion and functional imaging investigations of Stroop performance is response modality. Behavioral procedures employed with large patient studies most often involve verbal responses whereas button press responses are

typically collected in the scanner environment. However, the fact that ACC activation was not observed in the blocked context of the present study suggests that manual responses are not sufficient to evoke ACC activation in the Stroop task. It remains a possibility that task context and response modality may interact to produce ACC activation. To our knowledge, no study has evaluated response modality effects on blocked Stroop stimuli. However, Barch and colleagues (2001) directly compared verbal and manual responses in the same subjects using the same mixed presentation procedure and found that the contrasts to isolate conflict showed identical ACC activations regardless of response mode. They did, however, find response-specific activations in more dorsal regions of medial cortex outside of the rostral cingulate zone consistent with other studies of response modality (Husain, Parton, Hodgson, Mort, & Rees, 2003; Sumner et al., 2007).

It is important to explicitly note that the blocked context employed here entails several other important differences compared with blocked context found in clinical versions of the Stroop task. The current procedure involves a single-trial presentation that does not require visual scanning, that introduces a variable foreperiod prior to each stimulus, and that eliminates the opportunity to perceive or process (at whatever level) the neighbouring stimuli. While these factors may conceivably influence absolute task performance (i.e., overall RTs, errors), our data suggests that these variables are not crucial determinates of ACC participation in processing of incongruent Stroop stimuli.

ACC activation was primarily observed in the unblocked and uncued context and positively correlated with the size of the associated Stroop effect, indicating that subjects who had more difficulty selecting the less automatic response engaged this region to a greater degree.

An area involved in actively controlling processing would presumably show a negative correlation with the size of the interference effect, such that greater activity would indicate greater control and therefore, less behavioural effect. However, we observed the opposite effect. There are several potential explanations for this. Positive correlations between ACC activation and the interference effect have been interpreted in other studies as evidence for passive evaluative functions, such as conflict monitoring (MacDonald et al., 2000). According to this account, incongruent trials in the unblocked uncued condition would involve a greater amount of conflict because they are unexpected and thus strategic processes are less engaged. This pattern could also be consistent with a more specific error-detection hypothesis (W.J. Gehring, Goss, Coles, Meyer, & Donchin, 1993) on the understanding that errors and near-errors are most frequent on incongruent trials in unblocked, uncued contexts. It has also been observed that the ACC plays a role in arousal which increases in response to processing of difficult stimuli (Critchley et al., 2003; Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). It is also possible that this reflects a postulated energization function invoked during demanding tasks (Alexander et al., 2007; Stuss et al., 1995). The current paradigm does not allow us to differentiate between these hypothetical roles, but the location of ACC activation in the present study is similar, albeit somewhat lateral, to coordinates reported in studies that support an arousal role for the ACC (Critchley et al., 2003), whereas conflict monitoring and error detection manipulations tend to activate ACC regions in more superior and posterior areas of the rostral cingulate zone (Ullsperger & von Cramon, 2001).

The current data also confirm patient findings that superior medial frontal lesions are associated with impaired performance on blocked incongruent trials (Stuss, Floden et al., 2001). The Task PLS analysis showed a right superior medial cluster in the region of the SMA (caudal

BA 6, [20, -20, 67]) with negative saliences for LV design scores, indicating that activity in this region was associated with conditions that had negative design scores (i.e., the blocked context, see Figure 2). We have consistently found that superior medial lesions, particularly on the right, lead to increased errors and longer RTs on tasks requiring cognitive control (Alexander et al., 2007; Floden & Stuss, 2006; Picton et al., 2007). Based on that work, we have posited that this region is relevant for energization of task-related response sets. According to the theoretical model put forth by Stuss and colleagues (1995), energization is the mechanism that serves to activate task-related schemata that may entail information about task relevant stimulus attributes and/or associated responses. This function is necessary in contexts where non-routine response sets remain constant over an extended period of time and may wax and wane depending on endogenously-driven activation (as in blocked presentation of incongruent trials) (Kornblum, Stevens, Whipple, & Requin, 1999). It is less important in contexts where use of non-routine response sets is relatively rare or is externally cued (as in the mixed or cued conditions). The current activation data indicate that the superior medial region was related more to the blocked conditions of the fMRI task where we hypothesize an energization function would be most relevant. It is clear that ACC (BA 24 and 32) and more posterior and superior regions of the medial frontal cortex are not homogeneous but have dissociable roles in behavior selection (Picard & Strick, 2001).

The question remains as to why some studies in patients with ACC lesions do not show impairment on mixed versions of the Stroop. One possibility may be lesion laterality. In reviewing the literature, we found that the preponderance of fMRI studies, including the current investigation, reported right-sided activations during Stroop performance (Critchley et al., 2003; MacDonald et al., 2000; Ullsperger & von Cramon, 2001). Case studies and series that

demonstrate impaired Stroop performance after lesions have generally involved bilateral or largely right-sided lesions (di Pellegrino et al., 2007; Ochsner et al., 2001). Likewise, three of the four patients with intact Stroop performance in Fellows and Farah's (2005) study had exclusively left-sided lesions. The exception appears to be patient RN (Swick & Jovanovic, 2002; Swick & Turken, 2002) who has a left ACC lesion and showed significant Stroop impairment. However, RN was much older than other comparison subjects and has structural MRI evidence of significant cortical atrophy which could be contributing to his performance deficits. This argument for laterality is posthoc, and additional research is necessary to address this hypothesis.

A second possibility concerns compensatory changes that may occur following brain damage. It is possible that other brain regions are able to 'fill in' for the crucial function of the ACC in processing incongruent stimuli. In this scenario, at least one of two relationships might be expected in lesion studies: a positive correlation between lesion size and Stroop impairment, and a negative correlation between time since lesion and Stroop impairment. The current literature does not support the first relationship. Amongst the large group studies, only two include lesion descriptions beyond simple location. Vendrell and colleagues (1995) did not report lesion size for each patient but point out in their conclusions that very large left lobectomies were not sufficient to produce poor Stroop performance. In our prior study (Stuss et al., 2001) we included lesion size in the analysis and did not find any relationship between Stroop impairment and lesion size. Likewise, the patients reported by Fellows and Farah (2005) had medial lesions of varying sizes but all performed similarly to the control group. The second potential relationship is more difficult to evaluate given that lesion studies are typically performed with patients in the chronic stage of recovery from focal injury. The notable exception to this rule is patient MT reported by Ochsner and colleagues (2001) who completed the Stroop

task two days before, and three days after, bilateral cingulotomy for treatment of intractable Obsessive Compulsive Disorder. Patient MT did not show a general decline in all attention demanding tasks from pre-operative to post-operative sessions, suggesting a selective deficit in controlled processing in the acute stages of ACC damage. The potential role of lesion chronicity in the relevance of ACC for controlled processing is intriguing and deserves additional consideration in future studies using methods to identify changing functional networks.

We also had a priori hypotheses regarding left dorsolateral frontal cortex. While bilateral dorsolateral and ventrolateral prefrontal activations in Brodmann areas 46 and 9 were also prominent in the Task PLS results representing incongruent trials in the unblocked uncued condition, only activation in left BA 46 was correlated negatively with the size of the Stroop effect in the unblocked uncued condition. The finding that subjects with smaller Stroop interference showed greater left DLPFC activation is consistent with the presumed role of this region in task setting and implementation of stimulus-response rules (Stuss et al., 1995; Thompson-Schill et al., 2002; Vallesi et al., 2009). The left dorsolateral region was also inversely related to ACC activation. Others have proposed that the ACC and left DLPFC constitute a functional network whereby the ACC produces feedback signals regarding the difficulty or failure of response selection which can act directly or indirectly to ‘strengthen’ the current stimulus-response rules implemented in left DLPFC and thereby improve subsequent response selection (Egner & Hirsch, 2005; Fassbender et al., 2009; Holroyd et al., 2004; MacDonald et al., 2000). Conceivably, such a network would be most relevant for incongruent trials occurring in an unpredictable context where stimulus-response rules are not automatic and cannot be activated in advance. In simple terms, this would result in a negative correlation between left DLPFC and ACC activity, such that adequate activation of the left DLPFC (task set)

would reduced the likelihood of negative feedback on response selection (ACC) whereas inadequate activation of the left DLPFC would increase the likelihood of negative feedback on response selection. The negative correlation observed here between these two regions is fully consistent with this hypothetical functional network.

It should be noted that incongruent trials in the cued context did contribute, albeit in a much smaller way, to the pattern of brain activations identified in the Task PLS. This could be consistent with Parris and colleagues (Parris, Thai, Benattayallah, Summers, & Hodgson, 2007) study of cued task switching where ACC activation were most salient to instructional cues rather than stimuli to be responded to. We cannot directly address this relationship here given that our task was not designed to isolate activations related to the cues. However, this should be addressed in future work. Nonetheless, the RT data showed a behavioural Stroop effect in the cued condition that was intermediate between the blocked context and the completely unpredictable unblocked, uncued context, even though each stimulus was preceded by a predictive cue. The most likely reason for this is that the cues for congruent and incongruent stimuli were identical ('CLR'). The rationale for this procedure was to ensure that preparatory processing was similar for these trial types. Arguably, the most efficient strategy in this situation was to preemptively set attention to the relevant stimulus attribute while suppressing the irrelevant attribute. However, it is possible that not all subjects adopted this strategy consistently or effectively. Indeed, inspection of the subject means revealed that three subjects showed larger Stroop effects in the cued than the uncued unblocked conditions. This may underlie the contribution of the cued condition to the LV design scores.

As a final observation, the current data provide evidence that the ACC activations observed here, and potentially in other studies, cannot be attributed to simple differences in

stimulus frequency or the effects of novelty or 'surprise'. Most previous studies have manipulated the need for cognitive control by varying the relative frequency of stimuli such that processing of the stimulus with the lower frequency is less automatic or 'primed' and therefore requires more controlled processing. This introduces a possible confound in the novelty of the incongruent stimuli. Here, congruent and incongruent stimuli occurred with the same frequency (25%) in the unblocked conditions. The fact that ACC activation was relatively specific to incongruent stimuli in an unblocked uncued context indicates that the activated network is not an artifact of stimulus frequency.

CONCLUSIONS

The current study provides evidence that task context is able to account for the lack of converging evidence from group lesion studies and fMRI investigations regarding the relevance of the ACC for cognitive control in the face of conflicting information. We have further proposed that laterality may be responsible for conflicting case reports. The present study also provides evidence for the relevance of the left dorsolateral prefrontal region in performance of the Stroop test. The finding that greater activation in this region during unblocked and uncued contexts is related to smaller interference effects is consistent with the hypothesized role of this region for task-setting. Moreover, the observed inverse relation between activations in left dorsolateral and ACC further suggests that these areas have complementary roles and are flexibly recruited depending on the task context. We are currently in the process of completing a study of task context in Stroop performance in a large sample of patients with frontal lobe damage. This will allow a closer examination of the specific cognitive deficits associated with damage to different nodes in the cognitive control network.

Acknowledgments: This study was funded by the Canadian Institutes of Health Research Operating Grant# MT 12853 (D.T.S.). The authors would like to thank A.R. McIntosh for helpful comments on the manuscript, as well as D. Derkzen, C. Gojmerac, and P. McLaughlin for their help with data collection, and anonymous reviewers for thoughtful suggestions. D.F. is now at the Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH USA.

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Table 1. Activation Clusters for Latent Variable 1

			Talairach				
Lag‡	Cluster region	BA*	X	Y	Z	Size†	Bootstrap§
Positive saliences/bootstrap ratios							
1	R Ventral Anterior N. Thalamus	-	12	-3	11	19	7.4
1	L Middle Frontal Gyrus	10	-36	43	13	19	5.8
1	L Precuneus	7	-28	-71	55	12	5.6
2	R Anterior Cingulate	32	24	28	13	11	7.0
2	R Caudate Body	-	12	13	18	10	6.9
2	L Cingulate Gyrus	31	-4	-30	31	15	6.4
3	R Inferior Frontal Gyrus	9	44	5	26	21	8.4
3	L Middle Frontal Gyrus	46	-51	28	24	11	6.8
4	R Middle Frontal Gyrus	46	51	40	16	10	8.0
4	R Superior Parietal Lobule	7	32	-68	48	15	7.9
4	R Caudate Body	-	8	1	15	20	7.8
4	R Inferior Frontal Gyrus	9	40	9	29	10	7.6
4	R Inferior Parietal Lobule	40	55	-44	43	15	5.5
5	L Inferior Frontal Gyrus	9	-51	21	25	27	8.8
5	R Middle Frontal Gyrus	46	-51	32	21	29	7.5
5	R Precuneus	7	24	-61	29	13	7.5
5	R Cingulate Gyrus	31	8	-30	31	18	5.8
6	L Middle Frontal Gyrus	46	-55	29	28	34	8.0
6	R Inferior Parietal Lobule	40	48	-48	47	15	6.4
7	L Inferior Parietal Lobule	40	-32	-49	36	12	12.0
7	L Cingulate Gyrus	23	0	-22	31	17	6.2
7	L Inferior Frontal Gyrus	46	-32	32	9	12	6.2
7	L Inferior Parietal Lobule	40	-55	-56	43	27	6.1
Negative saliences/bootstrap ratios							
3	R Middle Temporal Gyrus	19	44	-61	14	15	-10.0
3	L Postcentral Gyrus	40	-59	-22	23	15	-7.0
5	R Cuneus	17	4	-89	4	13	-7.0
6	R Paracentral Lobule	6	8	-32	53	17	-8.0
6	R Precentral Gyrus	6	20	-20	67	11	-8.0

‡ time period, in TRs of 2 sec each, after stimulus of peak Bootstrap Ratio.

* Brodmann Areas determined by reference to Talairach Daemon (Lancaster et al., 2000)

† number of contiguous voxels included in the cluster.

§ Bootstrap Ratio is an index of reliability across participants.

Table 2 SPM Results

			Talairach				
Lag‡	Cluster region	BA*	X	Y	Z	Size†	Zscores
1	R Medial Frontal Gyrus	6	8	6	51	150	6.74
1	L Anterior Cingulate Gyrus	32	-4	21	39		5.8
1	L Frontal Gyrus	6	-4	-1	63		5.62
2	L Middle Frontal Gyrus	9	-48	9	33	40	6.37
2	L Inferior Frontal Gyrus	44	-51	9	18		5.12
2	L Insula	13	-40	16	-1	54	5.94
3	L Inferior Frontal Gyrus	47	-44	19	-11		5.27
3	L Insula	13	-32	24	10		5.18
4	R Inferior Parietal Lobule	40	51	-37	46	10	5.41
4	R Parietal Lobule	7	36	-56	47	29	5.4
4	R Inferior Parietal Lobule	39	36	-60	40		5.33
4	R Inferior Parietal Lobule	40	32	-53	36		4.99
4	R Inferior Frontal Gyrus	45	40	20	3	14	5.21

‡ Time period, in TRs of 2 sec each, after stimulus of peak Bootstrap Ratio.

* Brodmann Areas as determined by reference to Talairach Daemon tool (Lancaster et al., 2000)

† Number of contiguous voxels included in the cluster.

Fig 1.

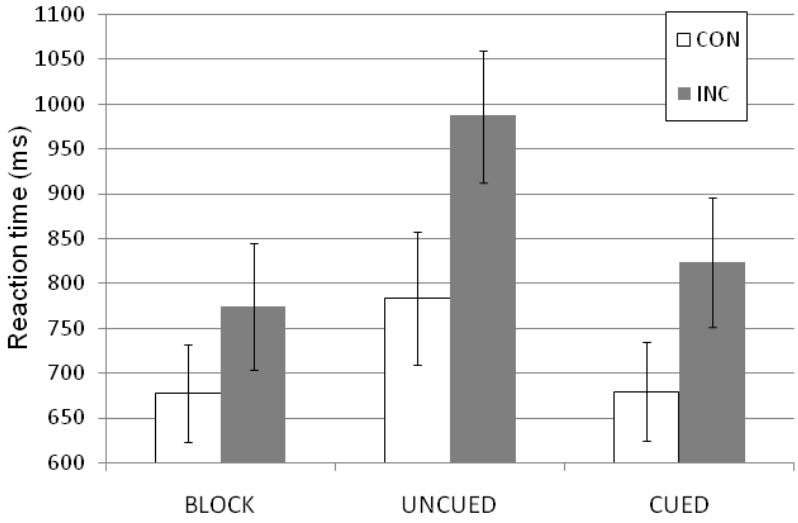

1100
1050
1000
950
900
850
800
750
700
650
600
Reaction time (ms)
CON
INC
BLOCK
UNCUED
CUED

Fig 2.

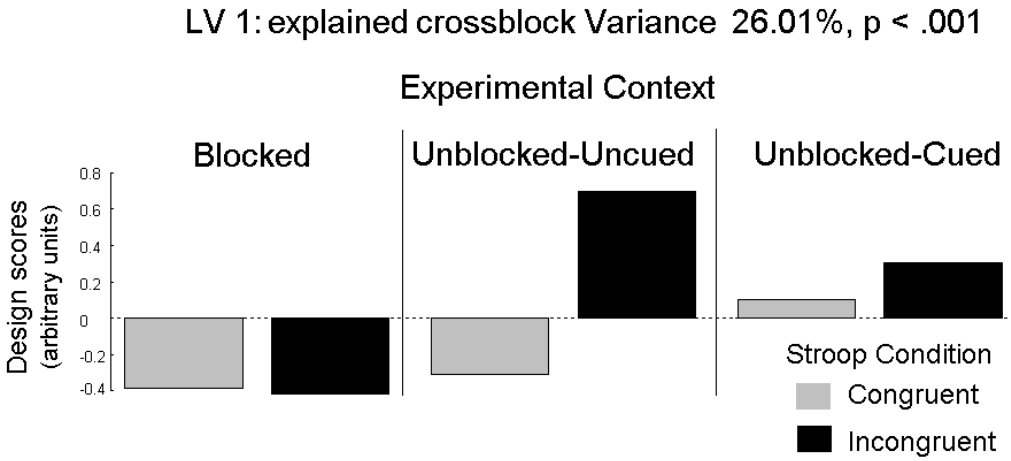
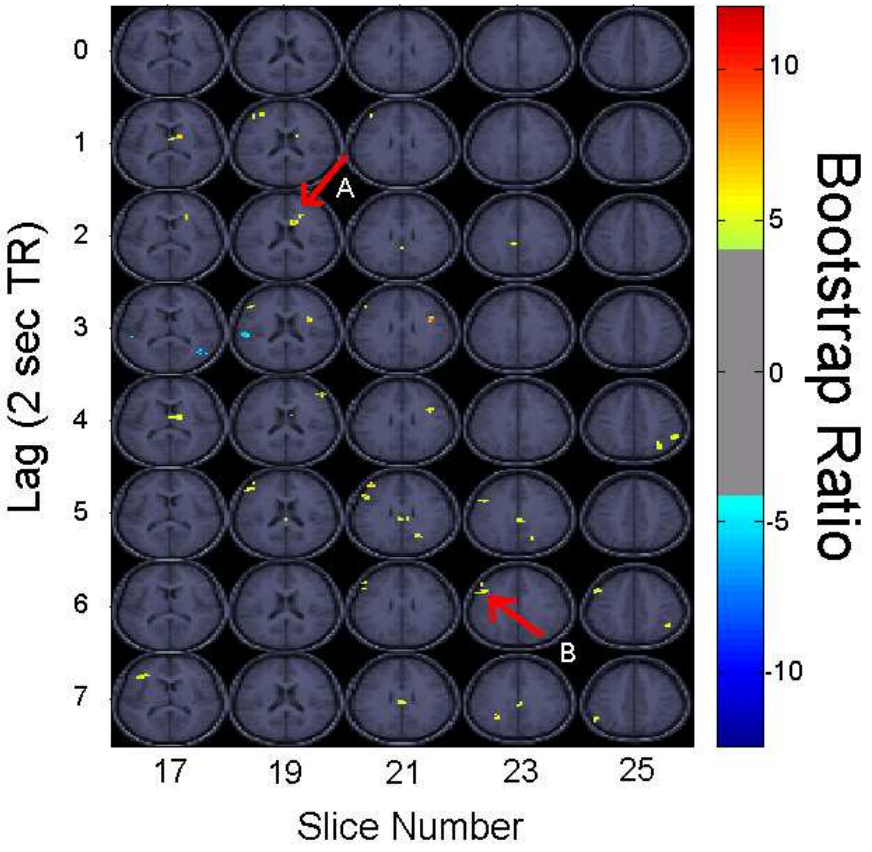

LV 1: explained crossblock Variance 26.01%, p < .001
Experimental Context
Blocked
Unblocked-Uncued
Unblocked-Cued
Design scores
(arbitrary units)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Stroop Condition
Congruent
Incongruent

Fig 3.


Lag (2 sec TR)
0
1
2
3
4
5
6
7
A
B
17
19
21
23
25
Slice Number
10
5
0
-5
-10
Bootstrap Ratio

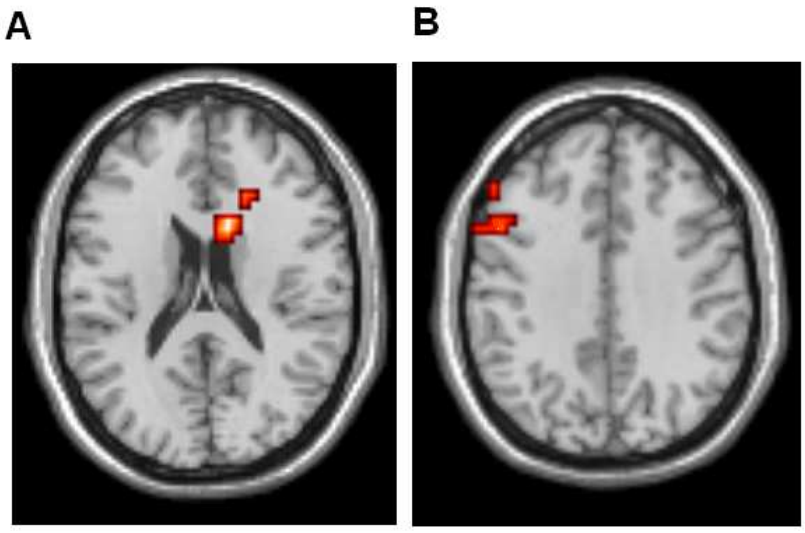

A
B

Fig 4.

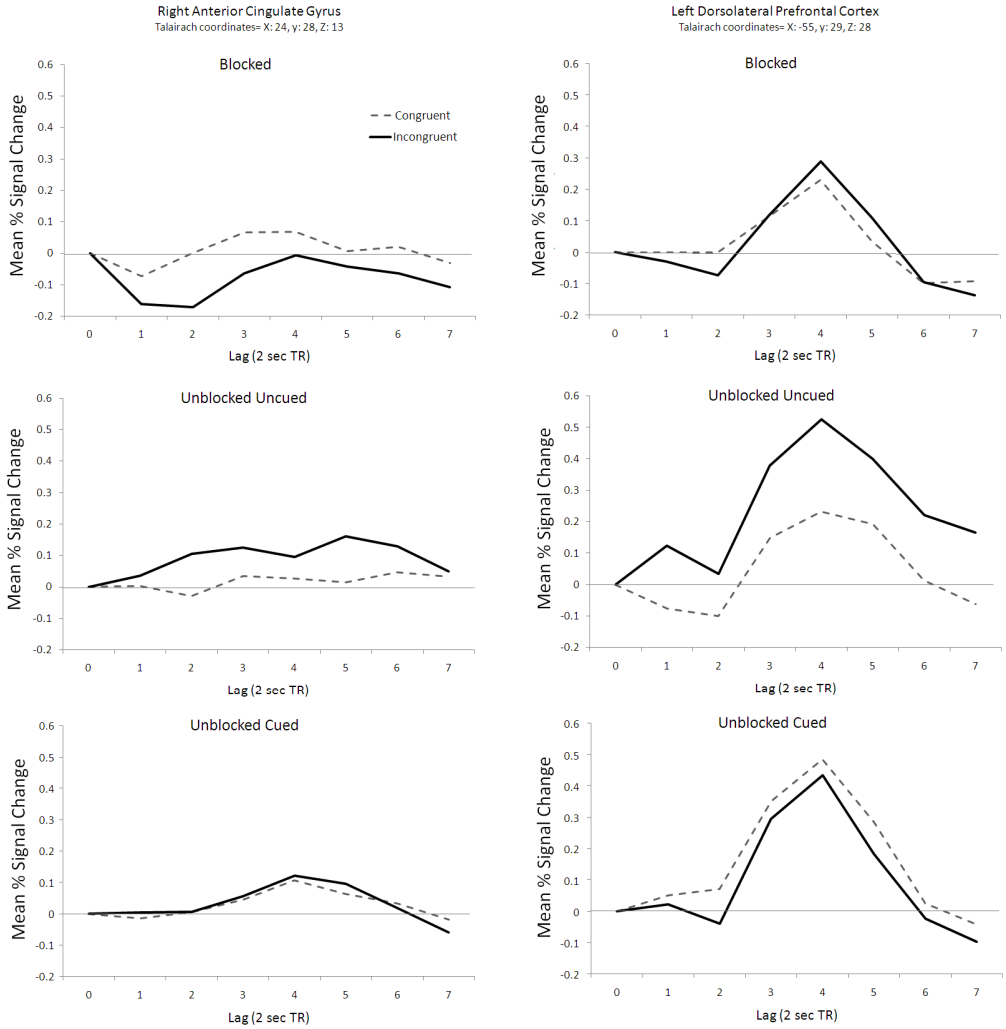

Right Anterior Cingulate Gyrus
Talairach coordinates= X: 24, y: 28, Z: 13
Left Dorsolateral Prefrontal Cortex
Talairach coordinates= X: -55, y: 29, Z: 28
Blocked
Congruent
Incongruent
Unblocked Uncued
Unblocked Cued
Mean % Signal Change
Lag (2 sec TR)

Fig 5.

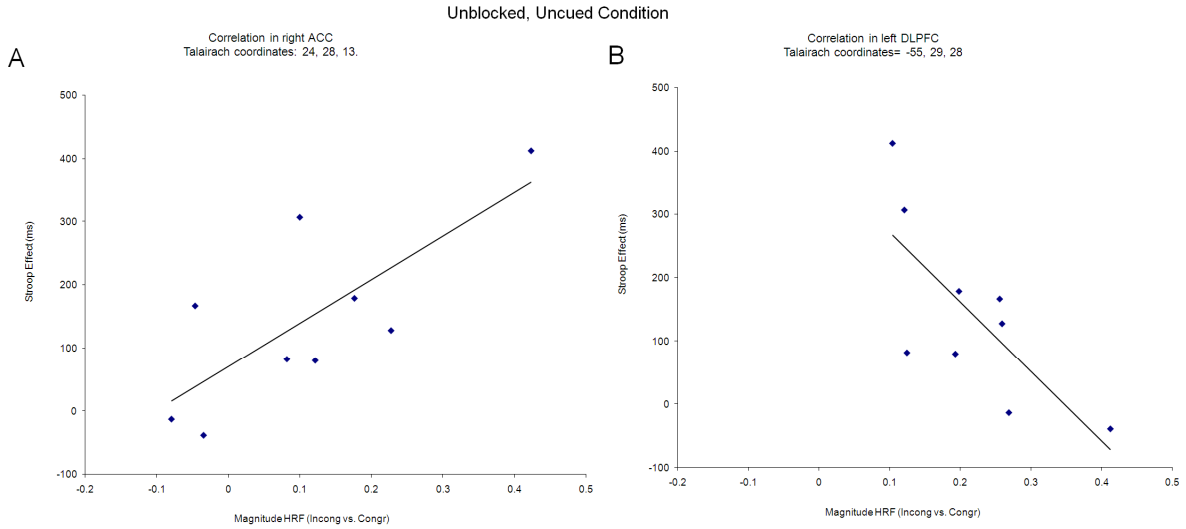

Unblocked, Uncued Condition
A
Correlation in right ACC
Talairach coordinates: 24, 28, 13.
Stroop Effect (ms)
Magnitude HRF (Incong vs. Congr)
B
Correlation in left DLPFC
Talairach coordinates= -55, 29, 28
Stroop Effect (ms)
Magnitude HRF (Incong vs. Congr)

Fig 6.