

## Functional connectivity during Stroop task performance

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Using covariance-based multivariate analysis, we examined patterns of functional connectivity in rCBF on a practice-extended version of the Stroop color-word paradigm. Color-word congruent and incongruent conditions were presented in six AB trials to healthy subjects during 12 H<sup>2</sup>O PET scans. Analyses identified two reproducible canonical eigenimages (CE) from the PET data, which were converted to a standard *Z* score scale after cross-validation resampling and correction for random subject effects. The first CE corresponded to practice-dependent changes in covarying rCBF that occurred over early task repetitions and correlated with improved behavioral performance. This included many regions previously implicated by PET and fMRI studies of this task, which we suggest may represent two “parallel” networks: (i) a cingulo-frontal system that was initially engaged in selecting and mapping a task-relevant response (color naming) when the attentional demands of the task were greatest; and (ii) a ventral visual processing stream whose concurrent decrease in activity represented the task-irrelevant inhibition of word reading. The second CE corresponded to a consistent paradigmatic effect of Stroop interference on covarying rCBF. Coactivations were located in dorsal and ventral prefrontal regions as well as frontopolar cortex. This pattern supports existing evidence that prefrontal regions are involved in maintaining attentional control over conflicting response systems. Taken together, these findings may be more in line with theoretical models that emphasize a role for practice in the emergence of Stroop phenomena. These findings may also provide some additional insight into the nature of

anterior cingulate- and prefrontal cortical contributions to implementing cognitive control in the brain.

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### Introduction

Stroop interference is undoubtedly one of, if not the most studied phenomena in cognitive psychology and remains at the cornerstone of investigations into human selective attention and the top-down control of behavior (Banich et al., 2001; Cohen et al., 1990; Miller and Cohen, 2001; Posner and Petersen, 1990). While many variants of the interference paradigm now exist (MacLeod, 1991), the basic principle that was made eponymous by Stroop (1935) is largely unchanged; that is, word reading—a highly prepotent learned ability—interferes with color naming. This effect is most striking when a color-word noun, for example, the word ‘RED’ is printed in blue ink and the task is to name the word’s color. Interference is characterized by the slowed response to naming these incongruent words compared to neutral- or color-congruent stimuli. Stroop facilitation on the other hand characterizes the speeded response to naming color-congruent words, for example, ‘RED’ printed in red ink, compared to color-neutral stimuli.

Popular connectionist models of the Stroop task have argued that interference and facilitation can be understood as inherent features of a parallel distributed processing (PDP) network, that is, ‘both reflect the outcome of the same competitive processes’

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(Carter et al., 1995), p. 226. Within this framework, overlapping (neural) pathways mediate word reading and color naming. Reading pathways have greater strength due to prior experience, which facilitates processing in color-naming pathways when color-word stimuli are congruent, but interferes with color naming when they are incongruent. Because word reading naturally holds precedence over color naming, attention needs to be biased towards weaker pathways for the naming of incongruent stimuli to occur. With practice, this response mapping can be learned and the relative strength of color-naming pathways can be increased (for a detailed description, see Cohen et al., 1990).

While this emphasis on emergent properties in PDP models has been recognized as crucial to their success in explaining Stroop phenomena (MacLeod, 1991), it remains unclear how such processes translate to neural systems that are involved in performing this task. The strongest evidence for an anatomical basis to the Stroop effect comes from PET and fMRI studies in healthy subjects (e.g., Carter et al., 1995; Leung et al., 2000; Pardo et al., 1990; Peterson et al., 1999). Most recently, these studies have focused on anterior cingulate (ACC) and dorsolateral prefrontal cortex (DLPFC) as responsible for implementing cognitive attentional control during Stroop interference (e.g., Banich et al., 2000; MacDonald et al., 2000; Milham et al., 2001). This work has addressed theories of ACC function related to conflict monitoring (Botvinick et al., 1999, 2001; Carter et al., 1998, 1999, 2000; Cohen et al., 2000; Kerns et al., 2004); error detection (see reviews by Bush et al., 2000; Gehring and Knight, 2000); and response selection (Erickson et al., 2004; Milham et al., 2003a,b; Paus, 2001), as well as putative executive functions of the DLPFC (MacDonald et al., 2000; Miller and Cohen, 2001).

Though informative, these concepts are relevant to only a small number of sampled regions, where it is clear that Stroop performance engages many other functionally important sites, including inferior prefrontal and parietal cortices and visual association areas (Peterson et al., 1999). There are also apparent differences among regions in the nature of their optimized response to practice-based repetition on this task (Bench et al., 1993; Bush et al., 1998; McKeown et al., 1998; Milham et al., 2003b). Notably, an involvement of the ACC appears to decrease after periods of initial task performance relative to increased activity in DLPFC (Erickson et al., 2004). This finding has demonstrated more explicitly a suspected parcellation of function between these two regions in implementing cognitive control (Cohen et al., 2000). The aim of the current study is to extend observations of regionally specific adaptation on the Stroop task, but within the context of larger scale neurocognitive networks. This is intended to complement existing ideas of the functional neuroanatomy of Stroop interference while considering the theoretical implications of task practice in the emergence of Stroop phenomena.

Attempts to characterize large-scale networks during cognitive task performance have been reported in many PET and fMRI studies already (Bullmore et al., 1996; Fletcher et al., 1996; Frutiger et al., 2000; Horwitz et al., 1995; Moeller and Strother, 1991; Shaw et al., 2002). These studies have generally relied on multivariate statistical approaches to identify patterns of spatially correlated activity in scans—an approach now often called “functional connectivity” (Friston et al., 1993; for recent discussions, see Horwitz, 2003; Lee et al., 2003). This includes exploratory methods such as principle (PCA) and independent components analysis (ICA) and more model-driven techniques such as canonical variates analysis (CVA) and partial least squares

(PLS; for a review, see Petersson et al., 1999). While the benefits of covariance-based approaches over the standard univariate approach (i.e., general linear model; GLM) are known (Lukic et al., 2002), their mainstream application has been limited by comparison. This is largely because multivariate techniques have lacked in established methods for inferential testing; that is, they result in descriptive spatial image patterns or eigenimages, as opposed to the quantitative statistical parametric map (SPM; i.e., SPM99; Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). However, techniques now including CVA and PLS have been adapted to generate voxelwise variance estimates or *Z* scores, which allow for a direct comparison to results obtained with univariate approaches (Lin et al., 2003; Strother et al., 2002).

Currently, two studies have applied multivariate analyses to explore covariance patterns associated with Stroop interference. In one study, PCA was used to examine the correlation of regions on several eigenimage patterns that were hypothesized to represent specialized (anatomical) components in a PDP network (Peterson et al., 1999). (Perhaps consistent with the conflict-monitoring hypothesis, ACC subregions correlated on each eigenimage component supporting the proposed evaluative role for this region in monitoring response pathways (Carter et al., 1998). While this was an appealing study because it attempted to combine statistical and cognitive principles of connectionist processing, the authors comment on the potentially low reproducibility of their findings due to small subjects numbers per variables in the PCA. In addition, these findings make no comment on potential practice-related changes in activity that might be expected to alter the interpretation of some regions in their proposed network. This latter point is significant in view of findings from a single-subject validation study of ICA, which showed that medial frontal (ACC) and lateral occipital activities decreased across Stroop trials compared to sustained activities in DLPFC and parietal foci (McKeown et al., 1998). However, like PCA, ICA has traditionally been a noninferential technique, which makes comparing these two studies to the existing corpus of Stroop neuroimaging literature difficult.

In the present study, we attempted to combine the benefits of regional statistical quantification (i.e., SPM), with the benefits of covariance-based multivariate analysis to model functional connectivity during Stroop task performance. To achieve this objective, we used NPAIRS (nonparametric, prediction, activation, influence, and reproducibility resampling) to perform multivariate (CVA) resampling of PET Stroop activation data. For a detailed description of the NPAIRS framework, refer to Strother et al. (2002; [http://www.neurovia.umn.edu/incweb/npairs\\_info.html](http://www.neurovia.umn.edu/incweb/npairs_info.html)). Using NPAIRS, we aimed to test more explicitly which brain regions form spatially distributed networks involved in Stroop performance and what components of these networks demonstrate change associated with task practice.

## Methods

### Subjects

Nine healthy volunteers (seven male and two female; mean age  $27.4 \pm 9.1$  years) were recruited for the current study, which was approved by the Austin and Repatriation Hospital Human Ethics Committee. Subjects were all carefully screened for no history of neurological, psychiatric, or substance abuse disorders.

All subjects were predominantly right handed as assessed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and presented with normal visual acuity and color vision. The mean estimated IQ, using the National Adult Reading Test (NART; Nelson and O'Connell, 1978) was  $115 \pm 6$  (range = 105–123), and all subjects had received at least some tertiary-level education. Written informed consent was obtained from all subjects.

#### *Stroop task*

Subjects completed a practice-extended version of the Stroop color-word paradigm that has been previously adapted for use in PET and fMRI experiments (Bench et al., 1993; Pardo et al., 1990; Peterson et al., 1999). This consisted of sequential- congruent (A) and incongruent (B) condition trials where each trial corresponded to a continuous 60 s PET scan. Twelve trials were acquired in total using a 6AB task design. For each condition, 36 stimulus words were presented consecutively 3 mm above a fixation point (white cross) for 1300 ms (SI) with an interstimulus interval (ISI) of 350 ms. Subjects were not practiced on the task before commencing PET scanning.

Under the congruent condition, one of four words (green, red, yellow, and blue) written in lower case letters appeared with equal probability. In this condition, the color of the print and the meaning of the word were compatible. Under the incongruent condition, the same four words were presented; however, the color of the print and the meaning of the word were not compatible (e.g., the word 'blue' written in red, green, or yellow print). For the incongruent condition, all combinations of incongruent 'print color' and 'word meaning' were equally probable. The same instructions were given twice, once before the first scan trial (congruent condition) and once before the second scan trial (incongruent condition). Subjects were instructed to keep their eyes fixed on the central cross throughout the entire testing session and that words would appear above the fixation point. The task instructions specified that subjects attend to and name as quickly as possible the color of the print in which the word was written without reading the word. In this paradigm, the congruent Stroop condition serves as a "baseline" task to which the lower order processing of stimuli can be matched to "active" incongruent task condition, that is, when examining "higher order" effects of Stroop interference (for further discussion, see Peterson et al., 1999), pp. 1238–1239.

Both conditions of the Stroop task were presented on a computer monitor located approximately 30 cm from the subject while they were lying in position in the PET scanner. Voice onset latencies were recorded with a microphone that was fixed to the subject's mask and was not visible to the subject. Following the presentation of each stimulus, the latency of the subject's response was recorded. The software for presentation of stimuli and the recording of responses was written in-house and has a 1-ms resolution. Responses were also recorded with a portable tape recorder that was out of the subject's view. We determined the mean latency of subject's responses for each of the six congruent and six incongruent conditions. Responses that were not clearly recorded, were abnormally fast (<100 ms), or were abnormally slow (>1200 ms) were excluded from analysis, accounting for approximately 5% of total responses made. We also calculated the number of errors made during the 12 Stroop scan trials. These were defined as errors due to misses (omissions) and errors due to incorrect verbalizations (commissions).

#### *Data acquisition*

PET scans were obtained using a Siemens/CTI 951R ECAT PET scanner, which acquires 31 transaxial slices across an axial field of view of 10.8 cm. Head movement was restricted using a customized thermoplastic mask, and a transmission scan was acquired using a  $^{68}\text{Ge}/^{68}\text{Ga}$  rotating rod source to enable correction of the emission scans for self-attenuation in the subject's head. For each subject, an initial scan using a tracer  $\text{H}_2^{15}\text{O}$  infusion (100 MBq) was performed to determine the time delay from the commencement of infusion to detection of radioactivity in the subject's brain; typically 40–60 s. A 40-s  $\text{H}_2^{15}\text{O}$  infusion (mean activity per infusion =  $370 \pm 60$  MBq) was administered per scan using a highly reproducible automated water generator (Tochon-Danguy et al., 1995). This produced a monotonically increasing brain count-rate for  $70 \pm 5$  s.

Twelve dynamic scans (six activation and six baseline scans) were acquired for each subject with the scanner operating in 3-D acquisition mode. Each scan consisted of two frames having durations of 30 and 120 s, respectively. Data from the initial 30-s acquisition frame were acquired to enable a background correction of the residual activity from the preceding scan to be applied to the data acquired in the second frame (foreground frame). The scan acquisition was commenced to synchronize frame—two with the increasing brain count—rate. The 60-s visual paradigm was presented 10 s before the commencement of acquisition frame—two, followed by 60 s of fixation during the residual decay of the foreground frame. The average radiation dose per subject was  $4.6 \pm 0.8$  mSv (Smith et al., 1994). PET images were reconstructed using a 3-D image reconstruction algorithm (Kinahan and Rogers, 1989) resulting in data volumes with  $128 \times 128 \times 31$  voxels (each of  $2.43 \times 2.43 \times 3.375$  mm<sup>3</sup>). A high-resolution T1-weighted MRI scan was also acquired for each subject (GE Signa 1.5 T scanner).

#### *Preprocessing strategy*

To minimize head movement artifact, spatial realignment of the individual PET images was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). Coregistration and spatial normalization was then performed using FSL (<http://www.fmrib.ox.ac.uk/fsl/index.html>). Brain extraction tool (BET) removed nonbrain matter (scalp editing) from each individual's T1-weighted MRI scan. FMRIB's linear registration tool (FLIRT) performed a two-stage coregistration process using linear, rigid body ( $df = 12$ ) transformations. This involved coregistering each subject's realigned mean PET image to their T1-weighted MRI, and then normalizing these coregistered images into standard neuroanatomical space (Montreal Neurological Institute; MNI-ICBM152).

An averaged group T1-weighted MRI from the subject's T1 images was used to mask out nonbrain activity following smoothing with a 3-D 12 mm FWHM Gaussian filter in SPM99. This anatomical MRI was also used to display NPAIRS/CVA results.

#### *Statistical analysis*

##### *Behavioral*

Vocalized reaction times (RTs) and error scores were analyzed by comparing the first and last half of experimental trials using a

repeated measures analysis of variance (ANOVA) with the factors; condition (congruent; incongruent) by time (trials 1–3; trials 4–6). This was done to examine effects of practice over early and later stages of Stroop task performance as reported in recent studies (Erickson et al., 2004; Milham et al., 2003b). We also calculated trial-by-trial Stroop interference RT scores (i.e., incongruent–congruent conditions) and analyzed for change across early and later trials.

#### PET $rCBF$

To measure functional connectivity during Stroop task performance, NPAIRS/CVA was used to investigate the inherent spatial covariance structure of the PET images. For a detailed description of the NPAIRS package and its application to PET data, see Strother et al. (2002; see also Frutiger et al., 2000; Shaw et al., 2002). Initially, all scans were volume mean normalized (VMN) by dividing each voxel's value by the mean value across all voxels within the specified brain mask. The mean value from each subject's images was then subtracted from each voxel in their individual scans (mean subject removal; MSR). This preprocessing strategy is aimed to reduce individual subject differences while maximizing sensitivity to within-subject effects (Frutiger et al., 2000). NPAIRS then performed singular value decomposition (SVD) on this input data structure, reducing its dimensionality to the first 20 principle components (PCs). Twenty PC's were chosen based upon previous PET studies where this approach has resulted in superior spatial pattern reproducibility (Shaw et al., 2002; M. Shaw, personal communication). CVA was then performed on this 'denoised' data structure.

Using NPAIRS/CVA, data can be flexibly assigned to  $n$  separate classes according to the experimental effects of interest (Shaw et al., 2002). For this study, we grouped each scan into its own experimental class (i.e., 12 classes from the six congruent–incongruent AB pairs) to determine the principle sources of covariance in the PET data. This data-driven approach is also useful for exploring interactions between subject's brain state and time; an a priori effect of practice that we anticipated from cognitive theory and neuroimaging studies of the Stroop task. Motivated by the results of this 12-class model, we then performed a more confirmatory two-class CVA, classifying each scan by brain state, that is, averaging congruent versus incongruent trials (see further).

The canonical variates (CVs) produced by NPAIRS can be described as maximizing between-class covariance in the data relative to the within-class error covariance (i.e., signal-to-noise), enabling the identification of experimental effects (Strother et al., 2002). CVs are derived successively until the full dimensionality of the between class covariance is represented (up to  $n - 1$  classes) where the number of significant CVs reflects the number of significant (orthogonal) sources of covariance in the data. Corresponding canonical eigenimages (CEs) therefore reflect the spatial regions that are most important for explaining these sources of modeled covariance (Friston et al., 1996; Kustra and Strother, 2001).

For CEs in the present study, NPAIRS cross-validation resampling was used to determine the reproducibility of measured effects after 50 randomizations of the data using the class structures, 12 or 2. CEs from each of the split-half groupings were then correlated against each other in a scatter plot and PCA was performed on the voxel values defined by the two images. The projection of each voxel's value onto the major axis of the PCA

was then used to define the "reproducible" signal for that voxel. Projections on the minor axis of the PCA defined an uncorrelated noise distribution, whose standard deviation gave a pooled variance estimate that is used to transform the voxelwise reproducible signal values into a  $Z$  score CE, or  $rSPM$ . The probability values corresponding to these  $Z$  scores are corrected random between-subject effects (Kustra, 2000). For the purposes of comparison to existing Stroop literature, we defined activity as significant if reaching a commonly reported peak height probability of  $P_{\text{uncorrected}} < 0.001$ .

For the two significant CV/CE dimensions that were identified, Pearson's product moment correlations (one tailed, simple regression) were calculated in Statistical Package for the Social Sciences (SPSS, version 11) between subject's CV scores and vocalized RT performances during the six incongruent trials (i.e., six points per subject). Although the validity of global performance metrics such as RT is limited in brain-behavioral models of practice or learning effects (Frutiger et al., 2000), RT responses on incongruent/conflict trials have been demonstrated to correlate with changes in brain activity on the Stroop task (MacDonald et al., 2000).

## Results

### Behavioral

Practice significantly improved subject's vocalized RT performances in the second half of Stroop trials compared to the first half of trials for both the congruent [ $F(1,8) = 9.29, P < 0.05$ ] and incongruent conditions [ $F(1,8) = 5.01, P < 0.05$ ]. While the magnitude of this change was not significantly different between conditions [ $F(1,8) = 2.16, P < 0.18$ ], the mean difference in RT performance during incongruent versus congruent trials corresponded to a significant Stroop interference effect [ $F(1,40) = 99.39, P < 0.001$ ]. Subjects performed with a mean RT cost of +186.1 ms (+23.4%) during the incongruent Stroop trials, which was unaffected by task practice [ $F(1,8) = 1.72, P < 0.23$ ]. Rates of error were low across the 12 AB trials; however, there was a trend for more errors to be made during the incongruent (11.9%) compared to congruent (3.5%) condition [ $F(1,8) = 3.75, P < 0.08$ ]. For both conditions, fewer errors were committed in the last half compared to the first half of Stroop trials [ $F(1,8) = 5.95, P < 0.04$ ]. Mean RT scores are presented in Table 1.

### NPAIRS/CVA

The 12-class CVA produced two CVs that accounted for most of the covariance in this model, Fig. 1a. The first CV (CV1) produced a canonical correlation of 0.94 and accounted for 49.6% of covariance. The second CV (CV2) produced a canonical correlation of 0.82 and accounted for 13.0% of covariance.

Table 1  
Mean reaction time (RT) performance

	Average	First 3AB	Last 3AB
Congruent RT	592.8 (76.8)	621.6 (88.2)	557.5 (58.4)
Incongruent RT	774.0 (60.6)	791.9 (61.2)	759.5 (61.8)
Interference RT	181.1 (64.9)	170.3 (85.9)	202.3 (46.5)
Interference (%)	23.4	21.5	26.5

Values in parentheses are standard deviations.

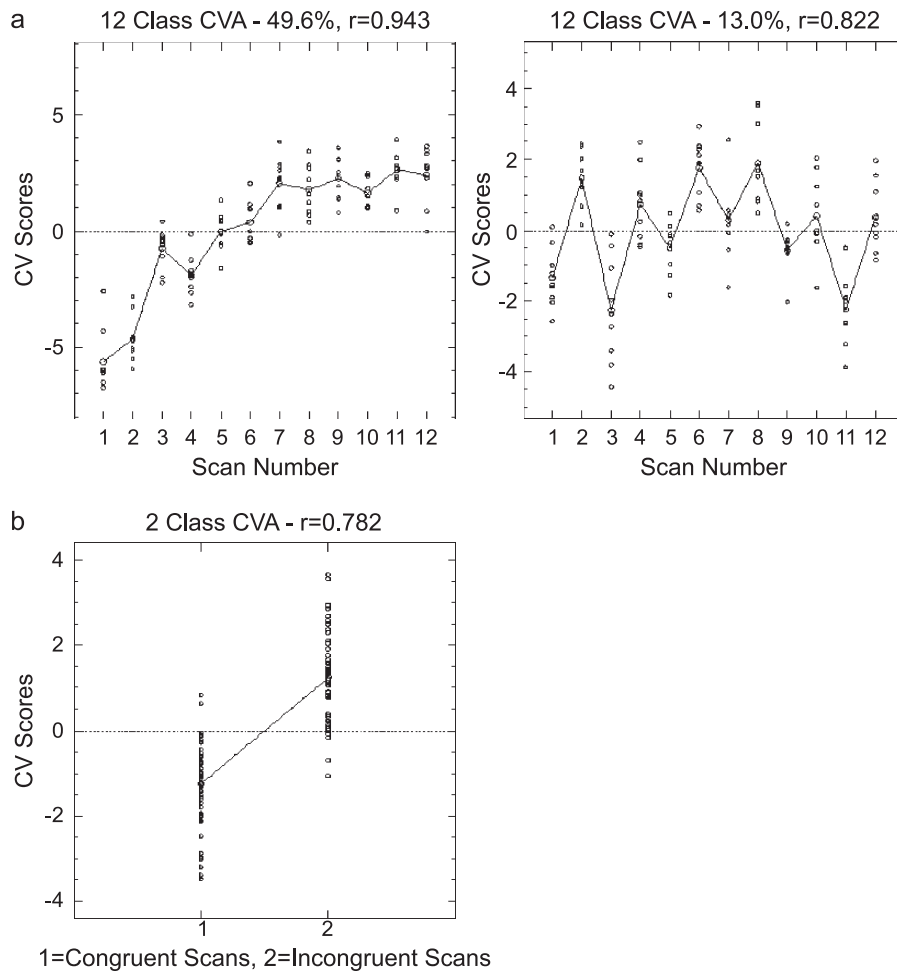


Fig. 1. (a) NPAIRS canonical subspace plots for the 12-class CVA model; left = CV1; right = CV2. (b) NPAIRS canonical subspace plot for the two-class CVA.

From Fig. 1a (left plot), it is clear that CV1 represents a monotonic effect of time across scans presumably due to task practice. This effect appears to be driven by changes in rCBF occurring over the first half of the experimental trials compared to latter trials. By contrast, CV2 reflects a difference between the scans belonging to the two experimental conditions, congruent and incongruent (Fig. 1a, right plot). To model this effect further, we applied the restricted two-class CVA model that averaged the congruent versus incongruent scans. This produced one significant CV with a canonical correlation of 0.78. From this canonical subspace plot (Fig. 1b), it can be seen that CV scores are uniformly higher in the incongruent versus congruent condition(s). The covariance discriminating between these conditions is therefore variance specific to incongruent task performance or “Stroop interference.”

For these results, we report on two canonical Z score eigenimage patterns (CEs; see Table 2). The first CE (CE1) corresponds to the “practice-related” effect identified by the 12-class model (CV1; Fig. 1a). The second CE (CE2) corresponds to the “interference” effect identified by the two-class model (Fig. 1b). Although there was no qualitative difference between the 12- and 2-class CVA results that represented this interference effect, Z scores in the 2-class CE were moderately improved by averaging the task conditions together as a simple linear discriminant function, that is, independent of scan-to-scan covariance, time/practice effects.

#### Eigenimage patterns

For CE1 (Figs. 2A and B), significant increases in rCBF that occurred primarily over the first three paired-task trials were observed in left inferior frontal cortex, bilateral primary motor and left supplementary motor areas, right dorsal/paralimbic and ventral anterior cingulate cortex, left posterior cingulate gyrus, bilateral lingual gyri, visual striate cortex, and left insula. For CE1, significant decreases in rCBF over the first three task trials were observed bilaterally in extrastriate cortex (fusiform gyrus) and the inferior temporal lobe, right medial temporal and parahippocampal gyri, left orbitofrontal cortex, bilateral superior frontal gyri, right thalamus, and left cerebellum.

For CE2 (Fig. 2A), significant increases in rCBF associated with Stroop interference were observed in the right orbital and medial frontal gyrus, left middle and lateral prefrontal cortex, left supplementary motor area, cerebellum, and right insula. For CE2, significant decreases in rCBF during interference were observed bilaterally in the medial temporal lobe, left inferior parietal lobe and right posterior cingulate cortex, left ventral anterior and subgenual cingulate gyrus, superior frontal gyrus, and cerebellum. While we report on canonical Z scores for this deactivation component in CE2, discussion of their functional implications will be limited.

Table 2  
 Canonical Z score activations for the 12- and 2-class CVAs

Significant activations approximate region	Brodmann area	Peak voxel-level activation			Z score
		x	y	z	
<i>CE1: Practice-related increases</i>					
Inferior frontal gyrus	11	-23	17	-20	4.25
Medial frontal gyrus	6	-6	-22	52	3.34
Precentral gyrus	4	-15	-32	54	4.09
	4	-46	-18	38	3.53
	3	34	-28	50	3.70
Anterior cingulate gyrus	4	40	-24	44	3.40
	32	6	0	40	3.33
	25	12	36	-18	3.23
Posterior cingulate gyrus	31	-11	-34	21	3.33
Lingual gyrus	18	-6	-96	-8	3.83
Striate cortex	18	4	-96	-10	3.53
	17	2	-100	-10	3.43
Insula		-40	-16	6	3.26
<i>CE1: Practice-related decreases</i>					
Fusiform gyrus	19	-30	-66	-16	5.25
	37	-42	-22	-22	3.75
	37	42	-46	-24	4.63
	37	52	-46	-22	4.21
Inferior temporal gyrus	20	-56	-42	-22	4.18
	20	52	-14	-28	3.60
	20	46	22	-20	4.94
Medial temporal gyrus	21	60	-44	-22	4.34
	21	46	1	-24	3.53
Parahippocampal gyrus	36	30	-20	-30	3.85
	28	20	8	-26	3.66
	36	28	17	-14	3.81
Orbital frontal gyrus	11	-8	17	-32	3.08
Superior frontal gyrus	10	-38	61	-2	3.44
	10	2	70	-10	3.24
	6	6	14	62	3.60
Thalamus		2	-8	8	3.09
Cerebellum		-34	-64	-24	3.82
<i>CE2: Interference-related activations</i>					
Orbital frontal gyrus	47	48	34	-16	4.39
Superior frontal gyrus	6	-6	6	58	3.99
Post central gyrus	3	-23	-28	58	3.78
Medial frontal gyrus	10	34	64	-10	3.72
Middle frontal gyrus	46	-42	16	18	2.99
Insula		32	-24	14	3.04
Cerebellum		6	-76	-35	4.90
		-62	-68	-30	4.41
<i>CE2: Interference-related deactivations</i>					
Temporopolar	38	-40	-8	-22	5.70
	38	24	-4	-30	4.42
Middle temporal gyrus	21	-52	-22	-14	3.70
	20	48	-12	-16	3.11
	20	46	-68	19	3.47
Angular gyrus	40	-42	-64	30	3.76
Precuneus	7	-1	64	35	3.09
Cuneus	30	-4	-70	6	3.24
Posterior cingulate gyrus	31	2	-32	36	3.95
Subgenual gyrus	25	0	14	-24	3.61
Anterior cingulate gyrus	32	-8	34	-8	2.99
Superior frontal gyrus	8	26	24	52	4.35
	8	-10	38	48	3.62
Cerebellum		44	-66	-42	3.47

NB: 12-Class CVA results = CE1; 2-class CVA results = CE2.

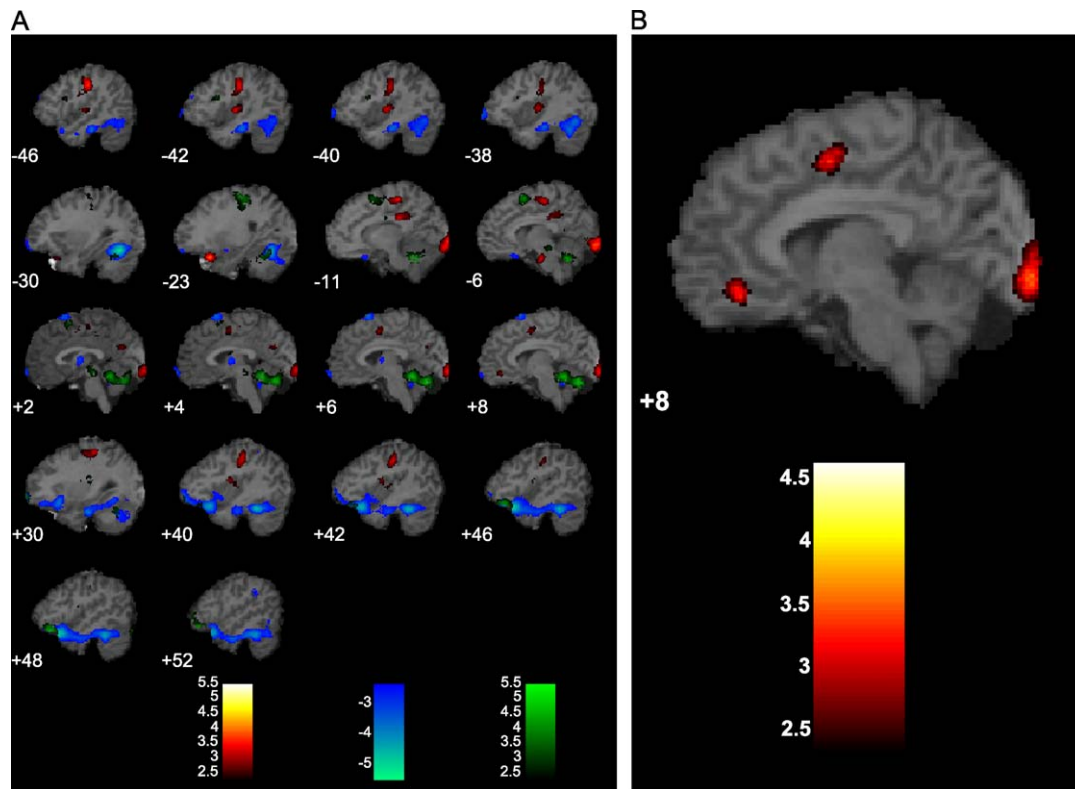


Fig. 2. (A) Reproducible Z score canonical eigenimage (CE) activations during Stroop task performance; sagittal plane view. Note: red scale corresponds to the first CE “practice-related” increases in rCBF; blue scale corresponds to the first CE “practice-related” decreases in rCBF; green scale corresponds to the second CE “interference-related” coactivations in rCBF. Negative  $x$ -plane integers = left hemisphere, positive  $x$ -plane integers = right hemisphere. (B) Canonical eigenimage (CE) one: early practice-related connectivity in rCBF at  $x = 8$ . Sagittal section of right dorsal and ventral ACC and striate/extrastriate cortex.

#### Correlational analysis of CV and behavioral scores

Post hoc analyses of imaging and behavioral results across the incongruent Stroop trials indicated significant and differential patterns of correlation between the two CV dimensions and subject’s RT performance. Overall, scores from the first CV dimension correlated negatively with RT ( $r = -0.33$ ,  $P < 0.008$ ) while scores from the second CV dimension showed a positive correlation ( $r = 0.28$ ,  $P < 0.02$ ). Further post hoc testing demonstrated that for CV1 this relationship was specific to the first three incongruent task trials ( $r = -0.47$ ,  $P < 0.006$ ) compared to the last three trials ( $r = -0.24$ ,  $P < 0.12$ ). The opposite relationship was observed for CV2, where CV scores correlated with RT performance in the last half ( $r = 0.38$ ,  $P < 0.02$ ) but not first half of incongruent trials ( $r = -0.04$ ,  $P < 0.42$ ). Thus, for CV1, where scores increased monotonically with time/practice, higher scores (i.e., denoting stronger covariance) were associated with shorter RT latencies (i.e., less interference) over the incongruent naming trials 1–3. By contrast, for the second CV dimension, where CV scores showed relatively minimal change across the six incongruent trials, higher scores were associated with longer RT latencies during incongruent trials 4–6 (See Fig. 3).

#### Discussion

Using combined multivariate resampling, we have identified two reproducible and dissociable patterns of functional connectivity associated with performance of the Stroop task. Consistent with

this study’s design, CVA characterized a strong practice-dependent change in rCBF that included many regions previously implicated by PET and fMRI studies of this task. This covariance pattern was shown to correlate with improved behavioral performance during early incongruent trials and we suggest may represent two “parallel” networks: (i) a cingulo-frontal system that was initially engaged in selecting and mapping a task-relevant response (color naming) when the attentional demands of the task were greatest; and (ii) a ventral visual processing stream whose concurrent decrease in activity may represent the inhibition of task-irrelevant word reading. The second CE that was identified corresponded to the traditional paradigmatic effect of Stroop interference. Coactivations were seen in dorsal and ventral prefrontal cortex, as well as distributed sites including the cerebellum. Unlike the first CE, this component represents activity that was intransigent to subject’s level of practice on the task, correlating with the magnitude of enduring RT interference in later practiced trials.

Despite a strong theoretical emphasis on the role of practice in the emergence of Stroop phenomena (Cohen et al., 1990), there are few studies to have examined potential neuroanatomical correlates of performance change on this task. Our results suggest that practice contributed a major source of covariance to the PET data that could be dissociated from the traditional Stroop interference effect. This is a novel finding because previous PET and fMRI studies of this task have utilized methods that only capture variances specific to this latter cognitive domain. Although this has been a valid approach, our results suggest that several regions demonstrated activities that would be poorly characterized by the standard GLM (subtraction) technique including high-order

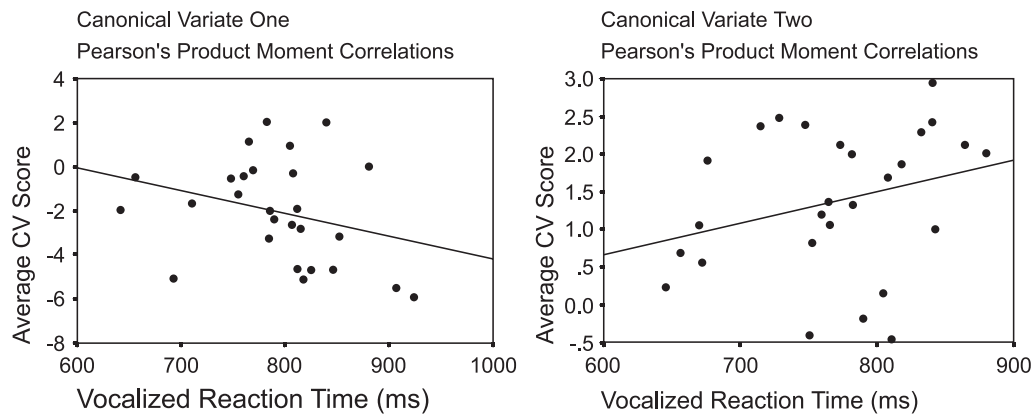


Fig. 3. Correlation of reaction time (RT) and canonical variate (CV) scores on incongruent naming trials. For CV1 (left plot), there is a significant negative correlation of RT and CV scores specific to first the three incongruent trials ( $r = -0.47$ ,  $P < 0.006$ ); while for CV2, there was a significant positive correlation of RT and CV scores specific to the last three incongruent trials ( $r = 0.38$ ,  $P < 0.02$ ).

regions such as the dorsal/paralimbic ACC and modulated lower order visual areas that are involved in general stimulus processing. These visual areas in particular may have value when interpreting modulated effects of task practice, as conceptually they form basic components of those “parallel” response pathways that are selected or inhibited during color naming versus word reading performance (Cohen et al., 1990).

Interpretively, the first CE corresponds to regions that demonstrated a covarying increase or decrease in their activities predominantly over early task trials and whose activities were associated with an improved color naming response as correlated on incongruent naming trials. Because CV scores were undifferentiated between the two task conditions and because RT performance improved generally as a function of task practice, this CE appears to represent common regions supporting the emergence of a strengthened behavioral response. This would align with the instructional set of both task conditions, which emphasized task-relevant color naming over task-irrelevant word reading. However, it makes intuitive sense that the nature of coactivations may be more characteristic of performance during the difficult incongruent trials (i.e., as indexed behaviorally by significantly longer RTs and more response errors). This is supported by a previous PET study, which demonstrated that when congruent and incongruent conditions were contrasted to color-neutral trials, respectively, both conditions showed a similar pattern of activated and deactivated regions (e.g., ACC, extrastriate visual areas) but a greater magnitude of evoked activity during incongruent task performance (Carter et al., 1995; see also Bench et al., 1993). Considering this, we suggest that the first CE reflects most parsimoniously activities that contributed to an improved color-naming response via processes of increased attentional inhibition as opposed to an improvement due to enhanced facilitation on color-congruent trials.

Corresponding to the first CE is a notable involvement of the ACC among a network of regions that increased in activity over early Stroop trials (Figs. 2A and B). The spatial distribution of this eigenimage pattern includes the right dorsal ACC activation that has been identified in previous Stroop studies (Bush et al., 1998; Carter et al., 1995; Kerns et al., 2004; Milham et al., 2003a,b; Yücel et al., 2002), as well as additional areas of the cingulate complex including ventral ACC and dorsal posterior cingulate gyrus. This pattern of functional connectivity is highly compatible

with the known anatomical connectivity of the cingulate regions (Vogt et al., 1995) and regions also demonstrating strong covariance, in particular, the primary and supplementary motor areas and left inferior frontal gyrus (Paus, 2001).

Coactivation of the posterior dorsal ACC and precentral gyrus may suggest an involvement of the cingulate motor system (Picard and Strick, 1996). This system has a recognized role in response selection processes and appears to activate in functional imaging studies irrespective of the response modality of the task at hand, for example, manual motor (Barch et al., 2001; Koski and Paus, 2000). There is also a recognized relationship between the ventral ACC and left inferior frontal gyrus that has been previously validated with PET and covariance-based connectivity analysis (Koski and Paus, 2000). The functional coupling of these regions is believed to form part of the neural circuitry responsible for vocalization (Paus, 2001), which has particular relevance to the current study where the mode of responding to Stroop stimuli was vocal, as opposed to the manual response paradigms often used in fMRI. It could also be speculated that coactivation of the posterior cingulate gyrus and left lingual gyrus may represent the task-relevant selection of color from the compound Stroop stimuli. Although the posterior cingulate gyrus has been largely implicated in visuospatial attention (Mesulam et al., 2001; Vogt et al., 1992), there is evidence that this region also participates in color form discrimination (Gulyas et al., 1994), while the left lingual gyrus is more commonly a region associated with the selective attentional processing of color (Corbetta et al., 1991; Lueck et al., 1989).

Involvement of the dorsal ACC in this predominantly cingulo-frontal network is of particular interest given its putative role in evaluative response processes, such as, conflict monitoring (e.g., Carter et al., 1998) and error detection (e.g., Gehring and Knight, 2000). Most recently, it has been suggested that the ACC monitors for conflict or error in response pathways during initial task performance, which contributes to the implementation of cognitive control in DLPFC when selecting between alternative responses is difficult (Milham et al., 2003a). This has hinged on observations during Stroop performance that the ACC is activated under conditions requiring response-level optimization as opposed to nonresponse (Milham et al., 2001, 2003a) and that activity within this region decreases as the level of response conflict/error is reduced with practice and/or control is established in DLPFC (Erickson et al., 2004; Milham et al., 2003b). Our results are not



inconsistent with this, although they indicate that habituation occurred only after this network initially increased in activity over early task repetitions. While this may relate to differences in the modeled variance between our study and previous studies, this may also suggest that the dorsal ACC formed part of a more distributed cingulo-frontal network that was involved in both response evaluation processes (i.e., conflict monitoring) as well as mapping or consolidating task-relevant responses when cognitive control was lowest. Though speculative, this is in keeping with the pattern of functional connectivity that we have described, that is, action monitoring in dorsal ACC; response mapping in posterior cingulate and visual cortex; and response execution (vocalization) via ventral ACC-inferior frontal cortex. Following these initial coactivations, regions such as the dorsal ACC may become less critically involved in this response network, while other and/or different regions may support the further consolidation (automatization) of naming responses with practice.

Central to our interpretation of the first CE is that practice on the Stroop task led to an improvement in RT performance related to increased inhibitory processing during early incongruent trials. Corresponding to the first CE are also regions that demonstrated a covarying decrease in rCBF with practice on this task. Though it is difficult to partial out nonspecific effects of task adaptation (i.e., due to decreasing emotional salience and stimulus novelty), we suggest that this reflects more specifically the inhibition of word reading responses within a ventral-visual processing stream. In previous studies, deactivation of the left lateral extrastriate cortex has been interpreted as a probable site for the inhibition of task-irrelevant processing on the Stroop task because of its hypothesized role in coding orthographic-lexical information (Carter et al., 1995; see also Buckner et al., 1995; Petersen et al., 1988). Additional areas of this CE also have hypothesized roles in processing word form and meaning, including the right fusiform gyrus and bilateral parahippocampal gyri (Corbetta et al., 1991; Demb et al., 1995; Price, 1998; Raichle et al., 1994). Therefore, at least conceptually, this practice-related decrease of functional connectivity within ventral visual regions supports the nature of competitive processing that has been advocated in PDP models (Cohen et al., 1990).

If this ventral stream holds true as a site of task-irrelevant inhibition on the Stroop task, then it begs the question as to what regions are responsible for generating this source of inhibitory control. It could be suggested that a reciprocal relationship exists between the “parallel” networks that we have described, where a cingulo-frontal system participates in task-relevant response selection or mapping and task-irrelevant response inhibition (Paus et al., 1993). However, in current models of Stroop performance, cognitive control is marshaled as a seemingly independent moderator of response pathways, either signaled into action by its own regulative mechanisms or in response to feedback (evaluation) from performance monitoring functions of the ACC (Botvinick et al., 2001). From recent functional imaging studies of this task, evidence has implicated the DLPFC as responsible for implementing this inhibitory bias over processing in posterior cortical regions (Banich et al., 2001; Milham et al., 2003a). This is illustrated well by Milham et al. (2002) who reported that in the event of less activation of the mid-DLPFC, and hence less inhibition of task-irrelevant processes, a more extensive activation of these same ventral regions occurred during Stroop interference.

Corresponding to the second CE, we note coactivations of the left DLPFC, right orbital frontal gyrus, and right frontopolar

cortex. These regions showed consistent task-related connectivity during Stroop interference, which was present at the behavioral level across the six incongruent trials. It was also found that this pattern most closely aligned with subject's RT performance during later incongruent trials, correlating with the magnitude of enduring response conflict. This pattern supports recent suggestions that the DLPFC “maintains” attentional control over Stroop performance after initial stages of response optimization with practice (Erickson et al., 2004; Milham et al., 2003b). The coupling of the DLPFC to other regions including orbital prefrontal and frontopolar cortex also suggests that such actions appear to engage a more distributed PFC network perhaps consistent with other recent studies of the functional anatomy of cognitive control (Badre and Wagner, 2004). It is interesting to note that the cerebellum demonstrated significant coactivation in this second CE pattern. The cerebellum has been previously implicated in studies of practice effects and automaticity in cognitive performance (Burnod, 1991; Grafton et al., 1992; Seitz et al., 1990) and typically shows decreased activity between unpracticed and practiced trials (e.g., Friston et al., 1992). However, that the cerebellum and frontal regions were engaged consistently by incongruent Stroop trials probably reflects that performance of the task remained effortful and never fully automatized, that is, hundreds of trials are typically needed to reduce the amount of RT interference (MacLeod, 1991).

In closing, the current study provides a novel characterization of the effects of practice and interference on functional connectivity in rCBF associated with performance the Stroop task. These findings largely compliment existing studies that have utilized this task to examine more specific roles for the ACC and DLPFC in cognitive control, although they suggest that the contribution of these regions is worth considering in the context of more distributed brain systems. Despite apparent consistencies between our results and results obtained with fMRI, there are obvious limitations to this study inherent with the use of PET (i.e., poor temporal resolution). For instance, our results do not comment on the dynamic adaptivity of the ACC and DLPFC regions during response conflict or error processing, which has been reported in recent event-related functional imaging studies (e.g., Botvinick et al., 1999; Kerns et al., 2004). The use of PET to examine extended effects of practice on this task also necessitated that we use a simple blocked paradigm of congruent and incongruent trials, which is not appropriate for modeling other response parameters such as Stroop facilitation effects. However, for the purpose of characterizing gradual changes in brain activity that may contribute to the reorganization of reading versus naming responses that emerge slowly with practice on this task (Cohen et al., 1990; MacLeod, 1991), we would suggest the current approach was sufficiently suited. A particular benefit of PET in this scenario was our ability to examine one of the basic tenets of true Stroop task performance, namely, vocalization. In fMRI studies of this task, subjects are often pretrained on alternative response parameters before scanning (e.g., button-box associations) because of the motion-artifact associated with vocalized movement. This practice may in turn lead to studies underestimating the responsivity of certain regions such as the ACC when averaging actual (scanned) task performances (for a recent discussion see Erickson et al., 2004). In the current study, practice not only contributed the greatest source of variance to our data, but it was those initial changes in activity resulting from practice that were arguably the most meaningful.

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