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Dissociable Executive Functions in the Dynamic Control of Behavior: Inhibition, Error Detection, and Correction

H. Garavan,*,† T. J. Ross,†,[1] K. Murphy,* R. A. P. Roche,* and E. A. Stein†,[1]

Department of Psychology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland; and †Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226

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The present study employed event-related fMRI and EEG to investigate the biological basis of the cognitive control of behavior. Using a GO/NOGO task optimized to produce response inhibitions, frequent commission errors, and the opportunity for subsequent behavioral correction, we identified distinct cortical areas associated with each of these specific executive processes. Two cortical systems, one involving right prefrontal and parietal areas and the second regions of the cingulate, underlay inhibitory control. The involvement of these two systems was predicated upon the difficulty or urgency of the inhibition and each was employed to different extents by high- and low-absent-minded subjects. Errors were associated with medial activation incorporating the anterior cingulate and pre-SMA while behavioral alteration subsequent to errors was associated with both the anterior cingulate and the left prefrontal cortex. Furthermore, the EEG data demonstrated that successful response inhibition depended upon the timely activation of cortical areas as predicted by race models of response selection. The results highlight how higher cognitive functions responsible for behavioral control can result from the dynamic interplay of distinct cortical systems. © 2002 Elsevier Science (USA)

INTRODUCTION

One of the most intriguing challenges faced by modern cognitive neuroscience is to explain the neural basis of higher cognitive functions, and particularly those involved in the executive control of behavior, while avoiding recourse to a homunculus or central controller. The dynamic control of behavior as characterized, for example, by task monitoring, error detection, and compensatory behavioral alteration, has been hypothesized to include several key prefrontal regions, including anterior cingulate and dorsolateral prefrontal cortex (Carter *et al.*, 1998; de Zubicaray *et al.*, 2000; Dehaene *et al.*, 1994; Garavan *et al.*, 1999; Gehring *et al.*, 1993). These executive functions are critical for flexible interaction with changing task or environmental conditions and their compromise, often labeled dysexecutive syndrome, has been implicated following brain injury and in clinical conditions such as schizophrenia, ADHD, and obsessive–compulsive disorder (Carter *et al.*, 2001; Casey *et al.*, 1997; Curtis *et al.*, 2001; Enright *et al.*, 1993; Pliszka *et al.*, 2000).

To elucidate the distinct roles played by different cortical structures in aspects of behavioral control, we created a demanding task context in which subjects had to exercise inhibitory control over their behavior by withholding a prepotent response. Inhibition is a critical component of behavioral control insofar as it enables us to overcome automatic or routine behaviors (Shallice *et al.*, 1993). Factor analytic investigations of executive functions have shown the primacy of inhibition in both clinical (Burgess *et al.*, 1998) and nonclinical samples (Chan, 2001) and previous functional brain imaging studies suggest that right hemisphere regions that include dorsolateral prefrontal and inferior parietal cortex and, medially, anterior cingulate cortex are especially important for inhibitory control (Braver *et al.*, 2001; Bunge *et al.*, 2001; de Zubicaray *et al.*, 2000; Garavan *et al.*, 1999; Konishi *et al.*, 1999; Rubia *et al.*, 2001). Efficient executive control also requires cognitive processes to identify when an error has occurred, a process critical to learning from a previous behavior and which appears to involve the anterior cingulate (Dehaene *et al.*, 1994; Kiehl *et al.*, 2000). However, if error-related activations are to be functionally relevant then they should be related to subsequent compensatory behavior (Gehring *et al.*, 1993), though *a priori* it need not be the case that the subsequent modification of behavior be implemented by the same structures that detected the error. Through the incorporation of individual differences and within-subject performance measures analyses, we have identified structures involved in inhibition, error detection, and behavioral correction, thereby dissociating these executive functions and revealing some of the dynamics of fluid behavioral control.

[1] Current address: National Institute on Drug Abuse-IRP, Neuroimaging Research Branch, 5500 Nathan Shock Drive, Baltimore, MD 21224.

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MATERIALS AND METHODS

Subjects and Task Design

Fourteen right-handed subjects (10 female, mean age 30, range 19–45), reporting no history of neurological or psychological impairment, completed a GO/NOGO task based on our earlier work (Garavan *et al.,* 1999) after providing written informed consent. The letters X and Y were presented serially in an alternating pattern at 1 Hz and subjects were required to make a button press response to each letter. Responses and response speed were recorded. Responses were to be withheld to lure stimuli: a lure occurred when the alternation was interrupted (e.g., the fifth stimulus in the train X-Y-X-Y-Y-X-Y). The event-related design of this experiment allowed the lures to be distributed unpredictably throughout the stimuli stream. To identify cortical areas critical for response inhibition and posterror processes, stimulus timing was individually tailored in an effort to produce an equal number of successful response inhibitions (Stops) and errors of commission (Errors) in each subject. Within the constraint of maintaining the stimulus onset asynchrony at 1 s (to ensure that session duration and stimuli numbers were equal for all subjects and to facilitate time-locking stimuli presentation to fMRI image acquisitions), we manipulated the stimulus duration within the 1-s window. Stimuli durations were 600, 700, 800, or 900 ms followed, respectively, by a 400-, 300-, 200-, or 100-ms fixation point. Subjects were instructed to try to respond while the stimulus was on screen. Prescanning testing identified the timing parameters that produced roughly 50% commission errors in each subject. During fMRI scanning, subjects completed four runs that contained 1180 targets (GO stimuli) and 80 lures (NOGO stimuli), resulting in an average interlure interval of 15.75 s.

Prior to scanning, subjects completed the Cognitive Failures Questionnaire (CFQ; Broadbent *et al.,* 1982), which provides a measure of everyday absentmindedness (scores range from 0 to 100 on this 25-item scale, with higher numbers indicative of greater absentmindedness). Behavioral testing with 23 novel subjects revealed the CFQ score to correlate positively with the Barrett Impulsivity Scale ($r = 0.52$, $P < 0.01$) (Patton *et al.,* 1995) and with the Dickman dysfunctional impulsivity score ($r = 0.63$, $P < 0.001$) (Dickman, 1990). The CFQ scores were used in correlational analyses with functional activation measures and subjects were also split into high- and low-absentmindedness groups based on a median-split of the CFQ scores.

Scanning Parameters and Data Analyses

Contiguous 7-mm sagittal slices covering the entire brain were collected using a blipped gradient-echo, echo-planar pulse sequence (TE = 40 ms, TR = 2000 ms, FOV 24 cm, 64 × 64 matrix, 3.75 × 3.75-mm in-plane resolution). All scanning was conducted on a 1.5-T GE Signa scanner equipped with a 30.5-cm i.d. three-axis local gradient coil and an endcapped quadrature birdcage radiofrequency head coil. High-resolution T1-weighted spoiled GRASS anatomic images (TR = 24 ms, TE = 5 ms, flip angle 45°, FOV 24 cm, thickness 1.0 mm with no gap, matrix size 256 × 256 × 124) were acquired prior to functional imaging to allow subsequent activation localization and spatial normalization. Foam padding was used to limit head movements within the coil. Stimuli were back-projected onto a screen at the subject's feet and were viewed with the aid of prism glasses attached to the inside of the radiofrequency head coil.

All analyses were conducted using AFNI v2.2 software (Cox, 1996). Following image reconstruction, the time-series data were motion corrected using 3D volume registration (least-squares alignment of three translational and three rotational parameters) and differences in slice acquisition times were removed using Fourier interpolation. Separate hemodynamic response functions at 1-s temporal resolution were identified for Stops and Errors. Although whole-brain acquisitions were acquired every 2 s, a deconvolution analysis with time locking to the locations of the lures within the 1-Hz stimuli stream (lures were equally distributed across the first and second halves of the 2-s image acquisition window) enabled the response functions to be calculated at this higher temporal resolution. The hemodynamic response functions were fitted to a γ-variate function using nonlinear regression as previously described (Garavan *et al.,* 1999). Brain activation was operationalized as the area under these event-related response functions expressed as a percentage of the area under the baseline. The baseline in this event-related design is an implicit one and is indicative of tonic task-related processing activity. Activation maps were warped into a standard stereotaxic space following established procedures (Talairach and Tourneaux, 1988) and spatially blurred (4.2 mm full-width at half-maximum isotropic Gaussian filter). Group activation maps for each condition were determined with one-sample t tests against the null hypothesis of zero event-related activation changes (i.e., no change relative to tonic task-related activity). Mean activations for clusters of significant voxels were subjected to between-condition and individual differences tests. Significant voxels passed a voxel-wise statistical threshold ($t = 4.7$) and were required to be part of a larger 100-μl cluster of contiguous significant voxels. The voxel-wise threshold was determined through simulations in which exact analysis procedures were repeated but the locations of Stops and Errors within the time series were randomly generated. The distribution of false positives derived from these simulations allowed us to calculate a critical t value with an omnibus 0.05 false positive probability level. This thresholding was also used for subsequent in-depth analyses involving recategorizations of the Stops and Errors (described next).

Inhibition Difficulty, Behavioral Compensation, and Success Prediction

We categorized Stops as being "difficult" or "easy" based on the speed of target (GO) responses that immediately preceded the successful inhibition, and analyses were repeated to calculate mean activation separately for each type of response inhibition. It was hypothesized that successful response inhibitions that followed fast target responses (determined by a median split of target response times that

preceded Stops) would be more difficult than Stops that followed relatively slow target response times.

To examine the neuroanatomy of compensatory behaviors, Errors were categorized as producing behavioral adjustment or not, based on the target response speeds that immediately followed the errors. A median split of response times to the first target that followed Errors was performed for each subject and activation was calculated for each error type. The slower half of these responses suggests trials in which subjects attempted to correct their behavior (i.e., became more cautious) so as to avoid future errors (Rabbitt, 1966). The faster posterror responses suggest that relatively less effort to change behavior occurred on these trials.

To examine brain states that precede lures, activation between 4 s prior to and 2 s after the lure presentation was summed separately for Stops and Errors and contrasted with a voxel-wise t test thresholded at $P < 0.01$ with a 50-μl cluster size criterion. More liberal thresholding was applied given the reduced power of this voxel-wise contrast and results should probably be considered exploratory.

ERP Study

Event-related brain potentials (ERPs) were recorded from a separate group of 20 normal participants performing the identical task under similar procedures (including individually tailored stimuli durations). Thirty-two-channel electrophysiological data were recorded in AC mode with a gain of 500 and a bandpass of 0.15–30 Hz. The A/D conversion rate was 500 Hz, and the range was 11 mV. Separate ERP waveforms were determined for target responses, Stops, and Errors. Latency analysis of ERP responses to Stops and Errors were of particular importance for the present study in light of the fMRI results (described below). Further methodological details and more complete results are reported elsewhere (Roche *et al.*, 2002).

RESULTS

Performance Measures

Analyses of the prescanning performance demonstrated that commission errors increased as stimulus durations shortened [$F(3,39) = 5.1$, $P < 0.005$], thereby supporting the efficacy of this task difficulty manipulation. During scanning, subjects made 36 ± 11 (mean ± SD) commission errors in response to the 80 lures (range 22 to 53), target response times were 338 ± 38 ms, and omission errors were rare (3 ± 4 of 1180). CFQ scores ranged from 16 to 54 and the means for the high- and low-absentmindedness groups were 37 and 21, respectively (two subjects tied at the median score were excluded).

The scanning performance data validated the categorization of lure difficulty based on prelure target response times. Errors were preceded by faster target responses than were Stops (319 ± 39 ms vs 363 ± 44 ms; $t(13) = 7.1$, $P < 0.0001$) and the percentage of commission errors following fast responses, based on a median split of all immediately preceding targets, was greater than the percentage of commission errors following slow responses (56 ± 16% vs 34 ± 12%; $t(13) = 8.6$, $P < 0.0001$).

Response Inhibition

Areas activated during successful response inhibition largely confirmed our previous findings (Garavan *et al.*, 1999), being predominantly right hemispheric and including frontal, cingulate, and parietal structures (see Table 1). Contrary to expectations, all these areas were also activated by commission errors (i.e., no area showed greater activation for Stops relative to Errors). It was hypothesized that successful inhibitions on this task depended upon the timely activation of response-inhibition brain areas. Consequently, commission errors would be due to a late activation, rather than an underactivation, of these same response inhibition areas. In support of this hypothesis, the ERP data revealed the temporal dimension of activation to be critical for discriminating Stops from Errors. Amplitude and latency differences were found in the N2–P3 complex for lures compared to targets at many electrode sites. The critical comparison for interpretation of the fMRI results is between Stops and Errors. P2 peak latencies were earlier for Stops over six electrodes (P4, CP4, TP7, TP8, FT8, F3) and, in keeping with the fMRI findings, no site recorded a larger amplitude for Stops over Errors. Similarly, P3 latencies were earlier for Stops at 11 mostly central/frontocentral and parietal electrodes while a larger P3 amplitude was found at just one site (F7, Stops > Errors). In the group-averaged waveforms, these latency effects were most evident for the right parietal sites as shown in Fig. 1.

Areas critical for response inhibition based on the fMRI data were observed once individual differences in absentmindedness were incorporated. Two-way ANOVAs (high/low CFQ × Stops/Errors) revealed significant interactions in just two of the regions that were activated for STOPS, the right middle frontal gyrus (BA 9) and right inferior parietal lobule (BA 40 and 7) (see Fig. 2). Low-absentminded subjects revealed greater activation for Stops over Errors, while high-absentminded subjects showed the opposite pattern (however, post hoc comparisons revealed only the low-absentminded subject contrasts to be significant). The implication is that subjects who are not relatively absentminded selectively activate this right parietal–prefrontal circuit when successfully inhibiting a prepotent response. High-absentminded subjects do not show this discriminant activation.

The comparison of easy and difficult inhibitions revealed opposite effects for bilateral anterior cingulate (ACC; BA 24, center of mass 2, −1, 45) and right dorsolateral prefrontal cortex (RDLPFC; BA 9, 46, and 6, center of mass 45, 15, 19) (these two areas plus a posterior cingulate cluster were the only ones to show difficulty effects). As shown on Fig. 2, the RDLPFC activated more for easy inhibitions, while the ACC activated more for difficult inhibitions [Region × Difficulty interaction $F(1,13) = 10.8$, $P < 0.006$; Difficult–Easy contrasts: RDLPFC $P < 0.003$, ACC $P < 0.0001$]. Activation in the anterior cingulate cluster for difficult inhibitions correlated with CFQ score ($r = 0.61$, $P < 0.02$), suggesting that the more absentminded subjects were more dependent on cingulate involvement. Faster response speeds were not the cause of the greater reliance of high-CFQ subjects on the ACC

TABLE 1

Areas Activated during Successful Response Inhibition (Stops) and Errors of Commission (Errors)

Structure	Brodmann area	Hemisphere	Volume (μl)	Center of mass		
				x	*y*	*z*
Stops						
Frontal lobe						
Middle frontal gyrus	9	R	838	44	−21	28
Precentral gyrus	6	R	1154	37	4	46
Precentral gyrus/inferior frontal gyrus	44	R	1130	50	−7	17
Cingulate gyrus/medial frontal gyrus	24/6	R	1996	6	−4	54
Cingulate gyrus	32	B	470	2	−18	39
	32	R	920	9	−28	32
	32	L	552	−6	−27	22
Inferior parietal lobule	40	R	1363	49	38	42
	39/7	R	193	33	56	39
Middle temporal gyrus	21	R	194	57	44	−2
Subcortical/insula						
Thalamus (medial dorsal and ventral anterior nuclei)		R	587	7	14	5
		L	1049	−11	13	7
Putamen		R	3011	23	−7	4
		L	802	−16	−1	6
Insula/claustrum	13	R	220	47	−12	−4
	13	L	809	−28	−14	5
Errors						
Frontal lobe						
Middle frontal gyrus/precentral gyrus	6	R	150	42	−1	42
Inferior frontal gyrus/precentral gyrus	9/6	L	642	−45	−2	31
Precentral gyrus	6	L	132	−19	7	53
Cingulate gyrus/medial frontal gyrus	32/24/6	B	5205	5	−10	46
Inferior parietal lobule	40	R	396	51	39	40
	40/2	L	128	−50	26	33
Middle temporal gyrus	22	R	106	58	43	4
	37/39	L	204	−49	58	5
Middle occipital gyrus	19	L	116	−50	67	8
Subcortical/insula						
Insula/claustrum	13	R	1282	38	−12	0
	13	L	1257	−32	−14	6
Putamen/caudate		R	1161	17	−8	4
Caudate		L	265	−6	−1	6
Thalamus (medial dorsal nucleus)		R	163	6	20	7
Thalamus (pulvinar)		R	127	8	29	1

Note. Positive values for *x*, *y*, and *z* coordinates denote, respectively, locations that are right, posterior, and superior relative to the anterior commissure.

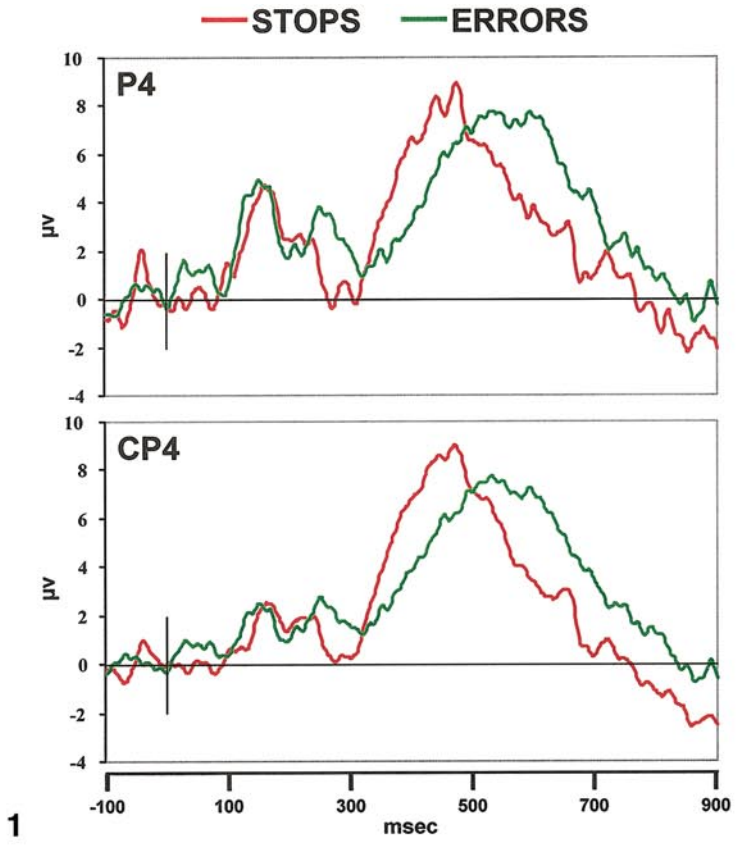
inhibitory system: CFQ score was not correlated with either overall target response speed ($r = 0.1$, ns) or preerror target response speed ($r = 0.09$, ns).

Error Detection

Areas activated on error trials included response inhibition areas (i.e., as described above, response inhibition activations that were too late to successfully stop the response) and behavioral correction areas (see below), as well as regions specific to error-related processes (see Table 1). Cortical areas activated specifically in relation to errors (including error-specific regions and regions involved in behavioral correction following errors) should show a greater response to Errors than to Stops, and the most prominent of these was a large bilateral midline area (incorporating the cingulate and medial frontal gyrus, BA 32, 24, and 6) (see Fig. 2). The remaining areas significantly more active for Errors than for Stops included inferior frontal gyrus, middle frontal gyrus, postcentral gyrus/inferior parietal lobule, and middle temporal gyrus in the left hemisphere and thalamus/pulvinar in the right hemisphere.

Behavioral Correction

Three areas showed significantly greater activation when behavior was “adjusted” relative to “not adjusted” following errors and showed greater activation for adjusted errors rel-



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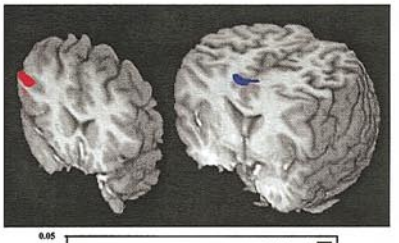
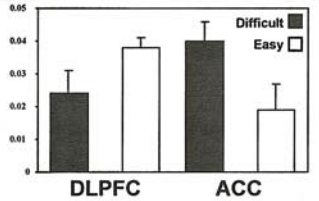
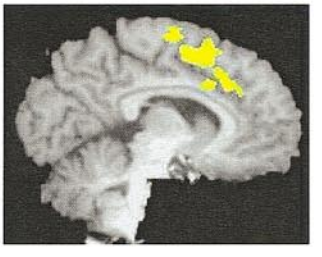
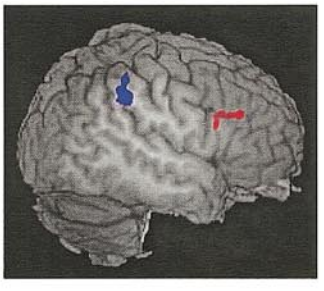




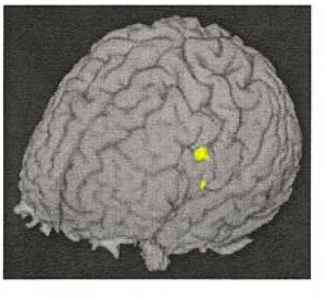
Inhibition Difficulty



Error Detection / Response Conflict



Low vs. High Impulsivity Response Inhibition



Behavioural Correction

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ative to Stops: bilateral ACC/pre-SMA (BA 32 and 24, center of mass 5, 14, 44), left inferior frontal and precentral gyri (BA 9 and 6, center of mass −46, 2, 21), and right putamen (center of mass 21, −12, 1). Of these three areas, the ACC/pre-SMA was the only one to show greater activation for both error types (i.e., whether behavior was subsequently adjusted or not) relative to Stops, underscoring its role in error-related processes. A one-way ANOVA (Stops, Errors with subsequent adjustment, Errors without subsequent adjustment) on ACC activation revealed a significant main effect [$F(2,26) = 8.2$, $P < 0.002$]. Post hoc tests showed adjusted Errors to be greater in activation than Stops ($P < 0.001$), unadjusted Errors to be greater than Stops ($P < 0.01$), and adjusted Errors to be greater than unadjusted Errors ($P < 0.008$). The remaining two areas showed greater activation relative to successful inhibitions only when behavior was subsequently slowed (i.e., Stops and Errors that did not produce compensatory response speed adjustments did not differ in activation), suggesting that their primary function was in behavioral adjustment and not in error detection.

A split-half comparison of subjects based on the magnitude of their response speed adjustment (mean adjusted response time − mean unadjusted response time) revealed that of the three regions implicated in altering performance, the left inferior frontal/precentral cluster [$t(12) = 2.7$, $P < 0.02$] was the only one to show greater activation in those subjects who made the greater adjustment (see Fig. 2).

Success Prediction

The contrast between the brain state that preceded Stops with the brain state that preceded Errors revealed two clusters of activation, one located in the culmen of the left cerebellum and one located in left dorsolateral prefrontal cortex (middle frontal gyrus, BA 9, center of mass $x = -41$, $y = -28$, $z = 32$), that showed greater activation preceding Stops [left DLPFC: $F(1,13) = 12.3$, $P < 0.004$].

Neuroanatomical Dissociation of Executive Functions

To confirm the apparent neuroanatomical dissociation of the executive functions isolated by the above analyses, a series of specific comparisons was performed on the functionally defined regions of interest.

First, areas implicated in response inhibition (right dorsolateral prefrontal cortex and right inferior parietal lobule) have already been shown to be more active for Stops than for Errors but only in those subjects scoring low in absentmindedness. When all subjects were included, Stops and Errors did not differ in activation. Instead, it was found that ERP latency was the critical determinant of success in inhibiting. It has also been shown that the analysis contrasting difficult and easy inhibitions for all subjects revealed an almost identical right dorsolateral prefrontal region that was more active for the easier inhibitions. Neither the right frontal nor the right parietal areas were involved in the response speed slowing that followed Errors; neither region differed in activation between adjusted Errors and unadjusted Errors [PFC, $t(13) = 1.2$, $P < 0.25$; IPL, $t(13) = -0.42$, $P < 0.68$]. The ACC area implicated in response inhibition, as already reported, showed greater activation for difficult inhibitions relative to easy inhibitions. This portion of the ACC lay more posterior to the ACC/pre-SMA region activated following errors with some overlap at the level vertical to the anterior commissure. However, despite this small degree of overlap, this more posterior ACC region did not differ in activation for Errors relative to Stops [$t(13) = 0.63$, $P < 0.54$] or for adjusted Errors relative to unadjusted Errors [$t(13) = 1.1$, $P < 0.29$], suggesting that it was involved solely in the inhibition process.

The more extensive ACC/pre-SMA region was significantly more active for Errors than for Stops. The comparison between adjusted and unadjusted Errors implicated an almost identical area involved in behavioral correction (i.e., greater activation when performance was slowed following an error). This region also had significantly greater activation for difficult inhibitions relative to easy inhibitions [$t(13) = 2.4$, $P < 0.03$]. Consequently, the ACC/pre-SMA region appears to have a broader executive function profile than the other regions of interest. Finally, a left prefrontal region was also associated with behavioral correction having greater activation for adjusted errors relative to unadjusted errors. In this region, unadjusted errors did not differ in activation to Stops [$t(13) = 1.2$, $P < 0.26$] and activation did not differ between easy and difficult inhibitions [$t(13) = 0.39$, $P < 0.70$], indicating a specific role for this region in posterror behavioral correction.

DISCUSSION

The present results suggest a triple neuroanatomical dissociation of executive functions and provide a step towards a topography of executive functions as depicted in Fig. 2. Right dorsolateral prefrontal and right inferior parietal areas were associated with response inhibition while a region of the cingulate was involved in “difficult” inhibitions. Left dorsolateral prefrontal cortex was activated when subjects ad-

FIG. 1. Averaged stimulus-locked ERPs (vertical dark lines identify stimulus presentation) for parietal electrodes for Stops (red) and Errors (green). The latency differences between the two similar waveforms confirm the importance of a timely activation for response inhibition.

FIG. 2. Cortical areas implicated in response inhibition, error detection, and behavioral adjustment. Response Inhibition: Top image demonstrates that the involvement of right dorsolateral prefrontal (red activation) and anterior cingulate (blue activation) regions in response inhibition depended upon the difficulty of the inhibition as defined by the speed of ongoing target response speeds. Bottom image shows dorsolateral prefrontal (red) and parietal (blue) cortical areas activated during response inhibitions in low-absentminded subjects. Error Detection: Midline areas (anterior cingulate and medial superior frontal gyrus) activated following commission errors. Behavioral Adjustment: Left prefrontal cortex was activated on error trials that were followed by a relative slowing of response speeds and was more active in those subjects who showed the greater slowing.

justed their ongoing behavior in response to an error. Finally, a midline area incorporating the anterior cingulate and pre-SMA was associated with most aspects of the present task's executive demands (difficult inhibitions, error-related processing, and posterror performance adjustment). The implications of these findings for our understanding of the neuroanatomy of executive functioning will be discussed in the following sections. It is important to note that this summary is also a simplification: while converging lines of evidence point to the importance of the particular structures indicated, each region in performing its executive function did so as part of a larger network of activated regions. While the sufficiency of the depicted regions to instantiate their respective executive function must yet be determined, the results, nonetheless, reveal a neuroanatomical fractionation of the central executive and complements other efforts to do so through cognitive tasks (Baddeley, 1996; Miyake *et al.*, 2000).

Prefrontal and Cingulate Roles in Inhibitory Control

Specific right hemisphere sites (middle frontal gyrus and inferior parietal lobule) appear to underlie successful response inhibition. To what extent these response inhibition areas underlie other aspects of inhibitory control is not clear, though it should be noted that right lateral prefrontal regions have been activated in countering proactive interference (Bunge *et al.*, 2001), set-shifting involving the inhibition of the previous rule in the Wisconsin Card Sorting task (Konishi *et al.*, 1999), response inhibition in the Stop paradigm (Pliszka *et al.*, 2000; Rubia *et al.*, 2001), and suppression of imitative behavior (Brass *et al.*, 2001), and a range of clinical disinhibition syndromes appear to follow from right hemisphere damage (Shulman, 1997; Starkstein *et al.*, 1997). However, despite the apparent importance of right-hemisphere-mediated inhibitory control, the present results suggest that it is but one of two neuroanatomical systems for response inhibition and that the involvement of these two systems can be dissociated based on the relative difficulty of the response inhibition. Specifically, when ongoing target response speeds were relatively slow, response inhibition was executed by the right prefrontal system. This inhibitory system may instigate a more deliberative or "controlled" inhibition, perhaps related to the right DLPFC's role in selecting (Rowe *et al.*, 2000) or switching to (Garavan *et al.*, 2000) the appropriate response (i.e., a nonresponse) over the prepotent motor response. Selecting an appropriate course of action in the face of competing or interfering demands is perhaps one of the defining functions of prefrontal cortex. Such a role for the right DLPFC is consistent, as described above, with its selective involvement in Stops for subjects who score low on absentmindedness.

The second inhibitory system, involving the anterior cingulate, was activated for inhibitions when ongoing response speeds were relatively fast, suggesting that this structure may be especially important in urgent inhibitions over faster or more automatic behaviors. Interestingly, the positive correlation between CFQ and the cingulate activation suggests that the more absentminded subjects were more dependent on this "urgent" cingulate involvement, a pattern opposite to that observed for the right prefrontal system. That the RDLPFC activation decreased for difficult inhibitions relative to easy inhibitions suggests that the cingulate's activation reflects a central rather than an incidental involvement in difficult response inhibitions. An alternative interpretation, that this more posterior region of the anterior cingulate was activating in response to increased response conflict but the response inhibition itself was being accomplished by the RDLPFC system, should predict increased activation in both structures for difficult inhibitions rather than the observed ordinal interaction. Furthermore, this region of the cingulate did not show greater activation for Errors relative to Stops as would be predicted if its activation reflected response conflict. Instead, this activation may be related to the role ascribed to cingulate motor areas in voluntary motor control (Dum *et al.*, 1993; Picard *et al.*, 1996).

Dissociable cingulate and lateral prefrontal roles in executive functions have been suggested previously (e.g., MacDonald *et al.*, 2000). A parametric manipulation of the ratio between GO and NOGO stimuli revealed RDLPFC increases and anterior cingulate decreases as inhibitory difficulty decreased, that is, as the relative numbers of NOGOs increased, thereby diminishing response prepotency (de Zubicaray *et al.*, 2000). In light of the present results, this is consistent with a hypothesized transition from reliance on the cingulate network to the dorsolateral prefrontal network to accomplish response inhibitions. Eventually, as the GO/NOGO ratio reaches 1:1, one might anticipate response selection to dominate, yielding dorsolateral prefrontal activation and minimal cingulate involvement as has been reported (Braver *et al.*, 2001; Konishi *et al.*, 1999).

When averaging over all subjects, no area showed greater activation for Stops relative to Errors. Given the difficulty of the task, due to the individual tailoring of the stimuli durations so as to increase commission error numbers, we hypothesized that appropriate response inhibition brain areas were activated for all lures (hence the activation of response inhibition brain areas for Errors) but that the timing of this activation was critical. The ERP data confirmed that the latency of the ERP response discriminated Stops from Errors as predicted. Consistent with "race" models of competing, independent response demands (Logan *et al.*, 1984; De Jong *et al.*, 1990), these results suggest that Errors occurred, not because of a failure of the relevant brain areas to activate, but because the inhibitory signal arrived too late relative to the signal to respond.

Error Detection and Behavioral Adjustment

The results support a central role for the anterior cingulate in error processing (Dehaene *et al.*, 1994; Gehring *et al.*, 2000; Kiehl *et al.*, 2000). Despite the inherent response conflict present for all lures, this error-related midline activation may reflect increased response conflict rather than a distinct process particular to the detection of an error, an interpretation which assumes that conflict was greater for Errors than for Stops (Botvinick *et al.*, 2001; Braver *et al.*, 2001; Carter *et al.*, 1998). Although the assumption that error trials contain particularly high levels of conflict has recently been challenged (Ullsperger *et al.*, 2001), this interpretation might explain the numerous executive functions for which

the present results have implicated the ACC/pre-SMA region. Error-specific activation, activation linked to subsequent behavioral correction, and activation associated with difficult/urgent response inhibitions may all reflect occasions on which particularly high levels of response conflict were detected (Botvinick *et al.,* 2001). The conflict monitoring theory would also predict midline activation for both Errors and Stops (Carter *et al.,* 1998) and the later ERP midline response for Errors relative to Stops (van Veen *et al.,* 2002) and provides a compelling theoretical framework for interpreting the midline activation results.

It should be noted that this midline area was quite large and incorporated both the ACC and, more superiorly, the pre-SMA. Recent data (Ullsperger *et al.,* 2001) suggest that error processes and response conflict monitoring processes may be neuroanatomically separable, with error processing associated with the cingulate motor area and response competition with the pre-SMA. Subsequent studies of our own with variants of the current task support this ACC/pre-SMA separation (data not shown; Garavan *et al.,* 2002). Others have reported a rostral anterior cingulate area that may play a role in error-specific processes (Kiehl *et al.,* 2000; Menon *et al.,* 2001; van Veen *et al.,* 2002) and while the midline activation of the present data did not extend as far rostrally and inferiorly as a peak activation reported by Kiehl and colleagues, it did extend into the rostral ACC area. Consequently, while the present data cannot unequivocally resolve which psychological function to attribute to the midline error-related activation, it is conceivable that it reflects both conflict monitoring and error-specific processes of distinct subregions.

While the present results have revealed a role for midline areas in both error-related processes and subsequent behavioral compensation (corroborating previous ERP results of Gehring *et al.,* 1993, and fMRI results of Carter *et al.,* 2001), the present data do show these two functions to be neuroanatomically dissociable. In particular, the left dorsolateral prefrontal area appeared to be involved in adjusting one's ongoing behavior given that this area activated only when response speeds slowed subsequent to Errors and not when response speeds remained fast. Furthermore, the magnitude of activation was greater in those subjects showing the larger response speed adjustment. Consequently, left prefrontal activations that have previously been reported to follow errors (Dehaene *et al.,* 1994; Kiehl *et al.,* 2000) may not reflect an error detection mechanism per se but instead a distinct behavioral alteration process that would typically be expected to follow errors.

Prefrontal Laterality

The hemispheric dissociation in DLPFC is notable. While right PFC was related to response inhibition, it was the left PFC that was involved in behavioral correction following an error. Adjusting one's behavior involves a shift in mental set which, in the current task, might involve slowing down, altering one's response criterion, becoming more attentive, and so on. A role mediated by the left PFC in establishing an appropriate task set has been shown by MacDonald and colleagues, who observed activation in this area when subjects were cued to prepare for a trial in which they would be obliged to overcome a prepotent response. (MacDonald *et al.,* 2000). The present findings provide converging evidence for the left DLPFC's role in maintaining an appropriate task set insofar as the amount of activation in this area preceding a lure predicted whether a Stop or an Error was to follow.

The separate roles for right and left dorsolateral prefrontal cortex in this task may explain why both prefrontal hemispheres have previously been implicated in inhibitory control. While the imaging data more consistently identify the right hemisphere with inhibition, the left appears to be important for certain aspects of inhibitory control such as combating intertrial proactive interference (Jonides *et al.,* 1998; D'Esposito *et al.,* 1999; but see Bunge *et al.,* 2001) and suppressing stereotyped responses in random-number generation (Jahanshahi *et al.,* 1998) and sentence completion tasks (Collette *et al.,* 2001). The tasks that appear to implicate the left prefrontal hemisphere may be those most dependent on maintenance of a tonic "inhibitory" task set (e.g., as one strives to keep trials distinct and self-generated responses from being too stereotyped) rather than phasic inhibitory acts (as epitomized by NOGO and STOP paradigm response inhibitions). Bunge and colleagues (2001) have recently reported that susceptibility to intertrial proactive interference correlated with left prefrontal activation. This result is consistent with a task set role for this region insofar as the correlations within a block of trials with high levels of intertrial interference did not differ for specific trials in which interference was present or absent. Instead, the activation in the left prefrontal region was present for the entire block of trials (both interference-present and interference-absent trials), suggesting a tonic rather than a phasic role in combating interference.

The interpretation of distinct roles for lateral prefrontal and cingulate regions in the control of behavior is consistent with a recent lateral prefrontal lesion study in which patients did produce an error-related negativity (ERN) following errors but were compromised in their ability to correct certain aspects of their behavior following errors (Gehring *et al.,* 2000). Interestingly, the ERN for these patients did not discriminate between correct and incorrect trials, being present after both. We speculate that the identification of an error and behavioral correction following errors may both be dependent upon active maintenance of an appropriate task set. Ongoing behavior can be compared against this task set, thereby allowing errors to be detected, and behavioral correction might be enacted through its augmentation.

CONCLUSION

The results underscore the importance of accommodating individual differences in interpreting functional activation patterns. Low- and high-CFQ subjects accomplish inhibition differently, such that high absentmindedness appears to be related to reliance on the anterior cingulate system rather than selective use of the right prefrontal–parietal system, a difference that was not driven by a confound in response speed between the two groups. These results may cast light on the nature of normal population variability in impulsivity

and the disruption of brain circuitry related to clinical conditions including hyperactivity, disinhibition, and drug abuse. Second, the results reveal the advantage of combining EEG and fMRI methodologies to reveal the temporal and topographical bases of behavioral control, having demonstrated that latency of a brain response can critically determine behavior. Finally and perhaps most importantly, the results reveal that the apparent fluidity of behavioral control is accomplished through the interplay of distinct cortical areas. This fractionation of executive functions enables higher cognitive control to be effected without positing a central controller. With a focus on prefrontal areas, the emerging picture is that overriding a prepotent response is accomplished by right dorsolateral prefrontal cortex (unless urgency is required, in which case the cingulate is involved), error and/or conflict processing is accomplished medially, and the maintenance of an appropriate task set, which is particularly active when one tries to modify behavior in response to an error, is accomplished by left dorsolateral prefrontal areas.

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