

Research report

A topography of executive functions and their interactions revealed by functional magnetic resonance imaging

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Abstract

We used fMRI to study the brain processes involved in the executive control of behavior. The Sustained Attention to Response Task (SART), which allows unpredictable and predictable NOGO events to be contrasted, was imaged using a mixed (block and event-related) fMRI design to examine tonic and phasic processes involved in response inhibition, error detection, conflict monitoring and sustained attention. A network of regions, including right ventral prefrontal cortex (PFC), left dorsolateral PFC (DLPFC) and right inferior parietal cortex, was activated for successful unpredictable inhibitions, while rostral anterior cingulate was implicated in error processing and the pre-SMA in conflict monitoring. Furthermore, the pattern of correlations between left dorsolateral PFC, implicated in task-set maintenance, and the pre-SMA were indicative of a tight coupling between prefrontally mediated control and conflict levels monitored more posteriorly. The results reveal that the executive control of behavior can be separated into distinct functions performed by discrete cortical regions.

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The control over routine, everyday behavior involves a number of complex executive processes including the maintenance of current goals, allocation of attentional resources, performance monitoring, inhibition of irrelevant stimuli or responses, detection of errors and the subsequent adjustment of behavior. Understanding how the brain instantiates these processes and brings them to bear on current task demands in a smooth and dynamic manner remains one of the challenges of cognitive neuroscience as well as a critical challenge for understanding and ultimately reducing human error. The following brief review of executive functions and their localizations within the brain reveals evidence for an

emerging map of distinct processes associated with distinct brain regions.

1. Executive functions and the brain

An essential part of the performance of any task is the maintenance of “task set”, i.e., a representation of task goals held in memory against which one can evaluate and monitor one’s performance. This function has been attributed to the prefrontal cortex (PFC) [3], particularly dorsolateral prefrontal cortex (DLPFC) [29,31,50]. One aspect of performance monitoring is error detection, which has been associated with behavioral adjustment in the form of posterior slowing in reaction times [64]. The detection of a characteristic error-related ERP component, the error-related negativity (ERN), present after participants make an error

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[34] and its proposed source localization in frontocentral regions has prompted a number of authors to associate anterior cingulate cortex (ACC) with an error-processing role [42,54,68,78,81].

However, it has been suggested that error detection may not be the sole trigger for performance amendment, but that the detection of conflict as caused by the simultaneous engagement of conflicting responses may be sufficient [7,8,50]. Monitoring of response conflict is also thought to be performed by ACC [4,10,15], so some controversy exists as to whether ACC is monitoring performance with respect to errors specifically, or more general response conflicts. Jonides et al [40] reviewed a number of different imaging studies investigating response conflict, using Stroop, flanker and GO/NOGO tasks and found ACC to be one of the few regions that the studies had in common. Recent data suggest that the two processes might be dissociated along the midline with rostral ACC involved in error detection per se and caudal ACC/pre-SMA being central to conflict monitoring [32,78,81]. A recent review of fMRI studies that attempted to separate conflict and error-related processes found that while error detection appeared to be subserved by the ACC, the focus of conflict-related activations appeared to be in caudal ACC/pre-SMA [37]. Jonides et al. [40] have made an interesting observation that conflict is usually only detected in tasks in which participants are distinctly aware of high levels conflict (e.g., the Stroop task or flanker tasks), whereas activation in the ACC is not normally observed in tasks in which response conflict is not under subjects' awareness (e.g., Jonides et al's [39] verbal working memory tasks). However, a recent study [59] utilizing Jonides et al's [39] verbal working memory task did find activation in ACC thereby calling into question the importance of explicit awareness of the conflict.

Botvinick et al. [8] have suggested that there is a reciprocal dynamic relationship between PFC, which maintains task set or enforces top-down control, and midline areas that detect conflict. These authors have suggested that midline conflict detection signals to PFC that increased levels of control are needed in order to perform the task efficiently. Increased levels of top-down control should then lead to decreased amounts of response conflict, as the system should be biased toward the appropriate response channel and away from the incorrect, conflicting response channel due to increased control.

Inhibition, while central to the control and regulation of behavior and impulses [26], is also important in controlling actions. Problems with inhibitory control have been implicated in a number of clinical syndromes [5,14,23,28,62] and in age-related cognitive decline [36,60]. Prefrontal cortical activity has been identified for NOGO events in monkeys [69] and Iversen and Mishkin [38] identified the prefrontal inferior convexity with inhibition in primates using the GO/NOGO paradigm. Some theories, however, have outlined models of executive control that do not

involve inhibition. Kimberg and Farah [43] and Kimberg et al. [44] have argued that the frontal lobes may be involved in storing and maintaining links between stimulus–response associations in working memory and that the problems associated with executive functioning in frontal lobe injury may be due to a collapse in connections between different representations in working memory. Akin to this theory, Miller and Cohen [55] have suggested that PFC is responsible for biasing the system toward making certain responses over others and that this is how cognitive control is achieved in the presence of competing stimuli. With this view of frontal lobe function, inhibition may be deemed theoretically superfluous, as choosing the more highly activated schema over competing but more weakly activated patterns of responding would be sufficient to control behavior. However, evidence for distinct inhibitory processes (i.e., schema or response suppression) have been provided for memory retrieval [1] and task sets [53]. Furthermore, factor analytic studies in both normal [17,56] and clinical populations [12] have identified inhibition as a dominant component of executive functions. Inhibition as measured by its factor score was also correlated with performance on a number of tasks that are commonly used to measure executive functioning (e.g., the Tower of Hanoi and Wisconsin Card Sorting Task) [12,17,56]. Finally, inhibition as a distinct construct has been linked with a number of clinical disorders such as ADHD [5] and Tourette's syndrome [61] and has also been shown to follow a different developmental trajectory than selective attention [6].

Functional brain imaging, while also implicating posterior brain areas, has confirmed the importance of PFC in inhibitory control. Bilateral, but predominately left hemisphere activation has been observed in block design GO/NOGO paradigms [24,67]. A possible limitation of block design studies, however, is that tonic processes, such as task set [25], as well as error-related processes are included in task activation maps. The inclusion of errors in activation maps has been demonstrated to substantially contaminate them and to confound between-condition contrasts [58]. Event-related fMRI designs are therefore more appropriate for studying discrete cognitive processes such as response inhibition as they can identify areas activated phasically at the actual moment of successful inhibition. Previous event-related designs have identified the right inferior frontal cortex (IFC) [2,45], right DLPFC [25,41] and right inferior parietal lobule (IPL) [10,30,31] in response inhibition. However, event-related paradigms also have limitations, in that they often compare NOGO with GO activation, which may not be optimal due to the different stimuli typically used for GO and NOGO events and the additional motor component involved in GO responses. The present study utilized a GO/NOGO task in which random unpredictable NOGO events could be compared with identical, yet predictable NOGO events, allowing us to conclude that inhibitory-related activation

could be attributed to the inhibitory processes per se rather than to the perceptual or motor demands of the NOGO event.

Critical to the implementation of these executive functions is the capacity to maintain an appropriate attentional state. While attention is a term which encompasses a number of separable yet interacting set of processes with very different utilities [21], sustained attention can be thought of as the maintenance of endogenous focus, usually to detect infrequent targets, over a given period of time, and hence is critical in the successful completion of many experimental paradigms as well as everyday tasks. Positron emission tomography (PET) [20,21,52,71] and lesion studies [84] have implicated right prefrontal and right parietal areas in this process.

2. The present study

Control over everyday behavior is underpinned by complex executive functions and errors in this control are revealed in absentminded action slips in normal—but particularly in frontally damaged—brains. The Sustained Attention to Response Task (SART) [65] has been shown to both predict the likelihood of such real life errors in normal and brain-damaged individuals, but also to be particularly sensitive to the presence of frontally impacting traumatic injury. In the Random SART, the digits 1–9 are presented in random order and subjects respond with a mouse click to each digit except 3 to which they must withhold their response. In the Fixed SART, the digits are presented in a repeating, ascending order (1, 2, 3, ..., 8, 9, 1, 2, ...) and subjects respond to all digits except 3.

The utilization of the Fixed SART as a comparison for the Random SART facilitates the investigation of a number of different processes. Both tasks require participants to withhold a motor response to the number 3. However, in the Random SART, inhibition of a prepotent motor response is essential as the requirement to inhibit responding is unpredictable, whereas in the Fixed SART the need to withhold a response is predictable and may therefore involve response selection rather than response inhibition per se. In the Fixed SART, participants are aware that a withhold event is approaching, and as opposed to executing a last minute “urgent” inhibition they are able to prepare a withhold response. We may conclude, then, that a comparison of Random vs. Fixed successful inhibitions to NOGO events may isolate response inhibition processes, with the Fixed SART acting as a response selection and visuomotor control condition.

Response inhibition may not be the sole function isolated by this comparison, however. The competition between the prepared GO response and the urgent requirement to withhold that prepotent response upon presentation of the NOGO stimulus in a GO/NOGO task has previously been shown to induce response conflict [10,32]. Response con-

flict is thought to occur when two conflicting response pathways or tendencies (here, the motor response itself and the need to withhold that response) are activated simultaneously. In addition, Logan and Cowan’s [47] race model, which proposes a “race” between the GO and the NOGO responses upon presentation of a NOGO event, would also support the existence of response conflict in its current definition. Therefore, successful withholds to NOGO stimuli in the Random SART can be expected to involve a degree of response conflict which will presumably be absent from successful withholds in the Fixed SART where individuals will have had time to prepare to withhold their response. Bearing this in mind, we might expect to see activation of regions that monitor for response conflict during successful inhibitions to Random NOGO events as well as regions that are involved in inhibition. From previous studies, we may anticipate that right prefrontal areas will be involved in inhibitory processes [2,10,16,30,31,46], whereas areas lying along the medial wall will monitor response conflict [4,7,10,15,31,37,78,80,82]. We may also expect to see both tonic activation in areas that detect response conflict and activation in areas that combat response conflict by enforcing top-down control.

Activation has previously been observed in the right DLPFC and right superior parietal lobe (SPL) when performing the SART [52] and this right hemisphere frontoparietal network has been implicated in sustained attention [20,21,71,84]. Error processing, believed to implicate ACC [42,54,78], can be investigated as commission errors are common in the Random SART. Some of these processes, such as sustained attention, are tonically active throughout the task; in other words, the need to maintain one’s endogenously driven attention is constant throughout. These tonic processes are best examined utilizing a block fMRI design. However, other processes such as inhibitory or error-related events are discreet, transitory events and hence require event-related analysis. Consequently, a mixed design (block and event-related) was utilized in order to identify tonically activated areas and areas that were active phasically, for conflict-related processes and for both successful and unsuccessful attempts to inhibit responding. We hypothesized that a right frontoparietal network would be tonically active reflecting sustained attentional processes. We also hypothesized that predominantly right hemisphere frontoparietal regions would be recruited during successful inhibitions to a NOGO. Midline areas were hypothesized to be involved in error detection and response conflict monitoring. More specifically, we expected to see ACC involvement in error detection and pre-SMA in conflict monitoring. Finally, given the proposed dynamics between response conflict and top-down attentional control [8,15,19,31,50] individual differences among participants were examined in order to evaluate whether or not there was evidence of a relationship between these two processes in the implementation of cognitive control.

3. Methods

3.1. Subjects

Seven male and 14 females with ages ranging from 19 to 37 and a mean age of 26.4 participated in this experiment. Three subjects were subsequently excluded from the analysis due to excessive movement. All participants were right-handed, were free of neurological disorders, psychiatric problems or head trauma and were not under any medication. Written consent was obtained from each participant and they were paid for their participation.

3.2. Sustained attention to response task (SART)

A modified version of the SART [65] that consists of a series of numbers from 1 to 9 presented in a random and unpredictable (Random SART) or sequential and predictable (Fixed SART) order was employed (see Fig. 1). Subjects responded by mouse click to every number except the number 3. Each digit was presented for 250 ms. In order to minimize response time differences between the Random and Fixed SART, a visual response cue of 50-ms duration with a poststimulus onset time of 100 ms (parameters based on Ref. [51]) was utilized. This response cue, a thickening of the poststimulus mask, appeared as a “visual blip”. Subjects were instructed to respond in time with this response cue and were trained before entering the scanner. The duration of the entire poststimulus mask varied (461, 572, 683, 794, 906 or 1017 ms) in order to sample different points in the haemodynamic curve as the NOGO stimulus

(the number 3) consistently fell after every ninth digit in the Fixed SART. Poststimulus duration changed after each full cycle (digits 1–9 in the Fixed SART and after each set of nine random digits in the Random SART). A distinct cue to indicate the onset of the next digit was presented during the final 400 ms of all poststimulus periods (see Fig. 1). NOGO stimuli were placed on average 12 s apart in the Random SART (ranging from 2 to 30 s apart).

Stimuli were presented and responses recorded using Eprime (Psychology Software Tools) in blocks of 90–92 s, which alternated with 30-s rest periods. Five blocks of Fixed SART comprised one run, and five blocks of Random SART comprised a second run and run order was counter-balanced across subjects. There were 36 NOGOs in the Fixed and 34 NOGOs in the Random SART of the 326 stimuli in each condition.

3.3. fMRI scanning

Scanning was performed on a 1.5 T Siemens scanner in which foam padding was used to restrict head movements. Sagittal slices (202 T₁-weighted) were acquired for each subject (slice thickness = 1 mm, field of view = 256 mm). Functional images were single-shot, T₂* weighted, echo planar imaging sequences. Twenty-two axial slices (5 mm slice thickness) were acquired for each subject (TR = 2000 ms, TE = 50 ms, flip-angle = 90°, 64 × 64 mm matrix size, field of view = 256 mm). Three hundred and five volumes were scanned for each run (Fixed and Random SART).

3.4. Image analysis

Data were analyzed using AFNI software [22]. Images were time-shifted using Fourier interpolation to correct for differences in slice acquisition time, edge-detected by removing any activation outside the brain and 3D motion corrected. Images or individual subjects that displayed excessive motion were excluded from further analysis, as were the first three images in each run. A mixed regression analysis was employed whereby tonic, task-related activation was calculated as a percentage change score using rest as baseline and separate impulse response functions (IRF) were calculated for correct inhibitions and commission errors. A nonlinear regression program determined the best-fitting gamma-variate function for these IRF [18,83]. The area under the curve of this gamma-variate function was expressed as a percentage of the area under the baseline (here baseline reflects tonic activation level, having first removed variance associated with task-related activation). These percentage area (event-related activation) and percentage change maps (block activation) were then warped into standard Talairach and Tournoux [73] space and spatially blurred using a 3-mm isotropic rms Gaussian blur.

Separate *t*-tests against the null hypothesis of no percentage activation change were then performed for Random and

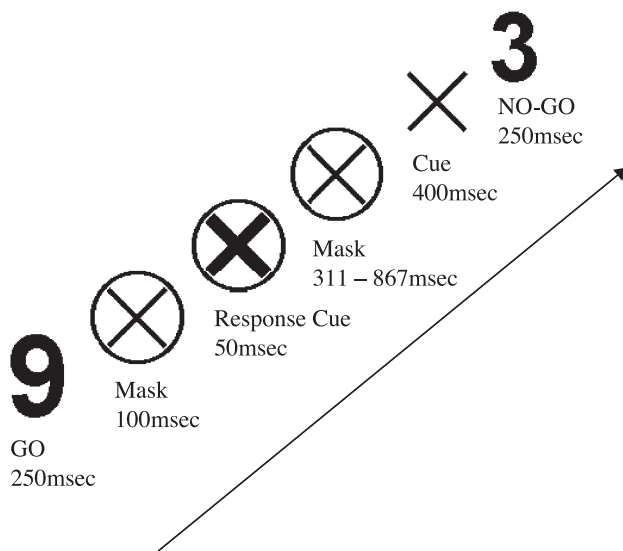


Fig. 1. An example of one cycle of the Sustained Attention to Response Task (Random) is presented. The variable poststimulus mask contained a response cue which appeared to participants as a visual “blip” in order to reduce reaction time differences that are typically found between Random and Fixed SART. A predictable prestimulus cue was also provided.

Fixed tonic activation and Random and Fixed correct inhibitions with a voxelwise threshold of $p \leq 0.001$ and a cluster-size criterion of 126 μl of contiguous significant voxels. These thresholds, determined by Monte Carlo simulations, resulted in a 0.05 probability of a significant cluster surviving by chance. Fixed and Random tonic activation maps were then combined into OR maps so that a voxel was included if it was significant in either map, and mean activation was then calculated for each of the resulting functionally defined regions of interest by condition. A similar procedure was employed for the Fixed and Random event-related, correct inhibition map. Differences between the SART conditions in these regions of interest were then tested with paired t -tests.

A slightly different method was used in order to make commission error maps due to the small number of errors in the Fixed SART. Percentage area maps for Fixed and Random SART were combined using weighted averaging (Fixed error activation multiplied by the number of Fixed errors plus Random error activation multiplied by the number of Random errors divided by the total number of errors) before t -testing against zero, resulting in one activation map for Fixed and Random errors combined. A more liberal p value of $p \leq 0.005$ combined with a cluster-size criterion of 126 μl of contiguous significant voxels was used for this map, as activations were absent at the level of $p \leq 0.001$. A widespread network of areas was activated for errors, including some areas that were also activated for successful inhibitions. Our previous research has shown that errors of commission on GO/NOGO tasks often include activated areas seen during successful inhibitions, which we interpret to reflect late, unsuccessful attempts at inhibition [31]. Consequently, areas specific to error-related processes were required to significantly differ in activation from successful inhibitions.

Interindividual correlations between activated brain regions were performed to determine the degree to which areas underlying executive functions interacted with one another.

4. Results

4.1. Performance results

Three subjects were excluded from the analysis due to excessive movement. The remaining 18 subjects (five male, mean age 26.5, range 19–37) had significantly more correct withholds in the Fixed ($90.2 \pm 9.8\%$) than in the Random SART [$71.47 \pm 16\%$; $t(17) = 6.06$, $p \leq 0.001$]. There were comparable numbers of errors of omission in the two conditions [7.28 ± 9.22 in the Fixed and 6.83 ± 9.68 in the Random SART, $t(17) = 0.17$, $p \leq 0.86$]. Reaction times are presented in Fig. 2. Although the commission errors in the Random SART followed a typical pattern for commission errors in GO/NOGO tasks

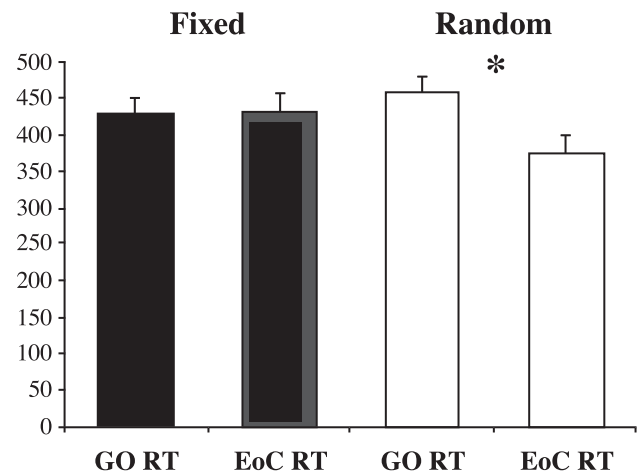


Fig. 2. GO event reaction times and commission error reaction times for the Fixed (F) and Random (R) SART, $*p < 0.001$.

in that they were significantly faster than response times for GOs [$t(16) = 4.121$, $p \leq 0.001$], this was not the case for errors of commission in the Fixed SART in which commission errors and GO response times did not differ [$t(15) = 0.350$, $p \leq 0.731$]. A 2 (correct inhibition vs. commission error) \times 2 (Fixed vs. Random SART) repeated measures ANOVA was carried out on these response times. Performance (correct vs. incorrect) and the interaction were both significant [$F(1,14) = 6.35$, $p \leq 0.02$; $F(1,14) = 7.46$, $p \leq 0.02$, respectively].

4.2. Block activation

A number of regions, visual, motor and frontoparietal were tonically activated during task performance (see Table 1). A subset of these areas was significantly more active for Random compared with Fixed SART and included pre-SMA, left and right putamen, left insula/inferior frontal gyrus (IFG), left precuneus, left parahippocampal gyrus and left supramarginal gyrus. No area showed significantly greater activation for the Fixed SART (see Fig. 3A).

4.3. Correct inhibition activation

Two distinct networks were seen to underlie correct inhibitions in the Fixed and Random conditions (see Table 2). The right ventral frontal cortex, right IPL, left DLPFC and the left putamen were significantly more active during correct inhibitions in the Random condition than in the Fixed condition, whereas the left IFG, right angular gyrus, left insula, and left middle frontal gyrus showed significantly greater activation during correct inhibitions in the Fixed Condition. No area was significantly activated for correct inhibitions in both the Fixed and Random SART suggesting that distinct networks were responsible for withholding a response in the two conditions (see Fig. 3B).

Table 1
Tonic activations for Fixed and Random SART

	Brodmann area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass)		
				x	y	z
				(RL)	(AP)	(IS)
<i>Frontal lobes</i>						
Precentral gyrus/MFG	6/9	L	1148	-43	0	32
Primary motor cortex	4	L	936	-40	-18	49
Premotor cortex	6	R	280	46	0	28
Median wall	6/32	B ^a	1022	-2	-1	49
Frontal operculum		L ^a	691	-43	8	1
<i>Occipital lobes</i>						
Occipital lobe (cuneus)	17/18/19	B ^b	15,668	-3	-67	6
Inferior occipital gyrus	17/18/20	R	5762	31	-80	-5
	17/18	L	3853	-30	-89	-5
Lateral occipital gyrus	19	L	2692	-42	-64	-8
<i>Parietal lobes</i>						
Intraparietal sulcus	7/40	R	592	28	-53	42
		L	629	-30	-46	40
Superior parietal lobule	7	R ^b	153	18	-53	62
Inferior parietal lobule	7	L	610	-33	-61	48
Paracentral lobule	4	R ^{ab}	385	5	-27	43
Supramarginal gyrus	40	L ^a	181	-42	-39	30
Lingual gyrus		L ^b	289	-24	-38	-11
<i>Subcortical regions</i>						
Precuneus	7	L ^{ab}	1079	-12	-46	47
Insula	41/42	R ^{ab}	824	39	-21	10
Putamen		R ^a	762	22	0	7
		L ^a	5238	-21	-8	7
<i>Cerebellum</i>						
Culmen		R	300	6	-55	-20

Note: inferior frontal gyrus (IFG); middle frontal gyrus (MFG); superior frontal gyrus (SFG); Left (L); Right (R); Bilateral (B). For *x*, *y*, *z* coordinates, R, A and S are positive.

^a Signifies that activation was significantly greater in the Random than the Fixed SART.

^b Signifies a deactivation in the Fixed SART.

4.4. Commission error activation

A combined (Fixed and Random) error map was constructed due to the small number of errors, particularly in the Fixed SART. These errors of commission produced widespread cortical activity (see Table 2). Activated areas included two regions in ACC and one in posterior cingulate, bilateral inferior frontal gyrus/insula and two left inferior parietal regions (see Fig. 3C).

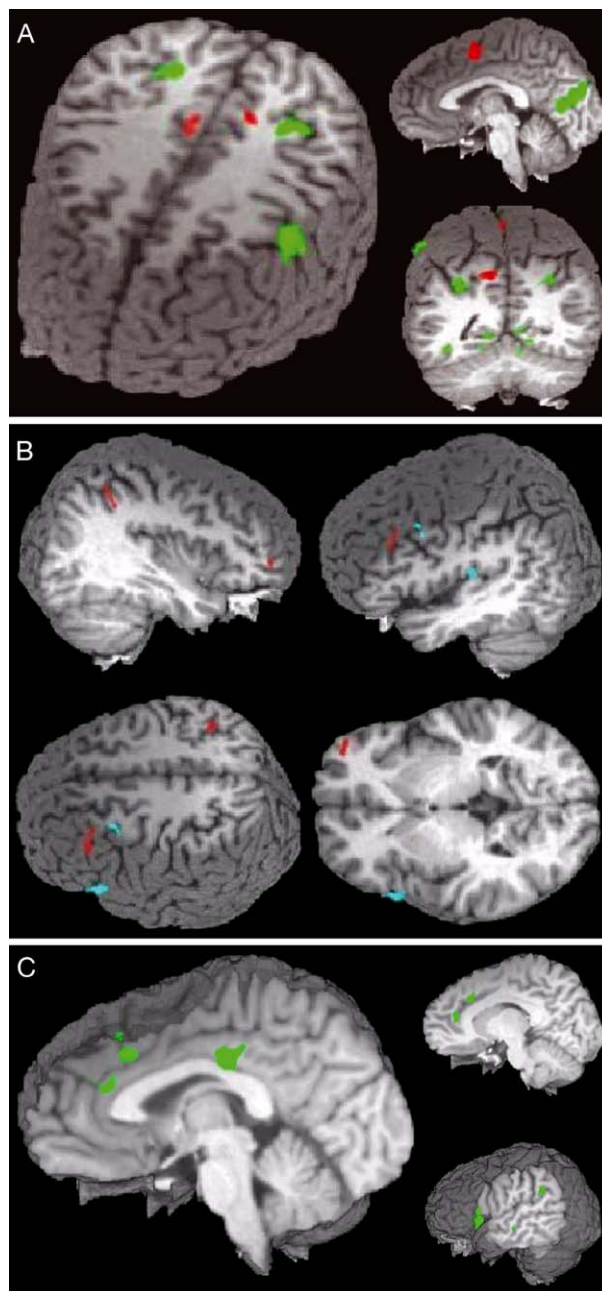


Fig. 3. (A) Tonic functional activation associated with the Random and both Random and Fixed SART. Areas in red that were significantly more activated for the Random over the Fixed SART included the pre-SMA and the right medial wall. Areas in green that were activated tonically in both the Fixed and Random SART and did not significantly differ between the two conditions included left dorsolateral prefrontal cortex, bilateral inferior parietal cortex and visual areas (bilateral cuneus and left lateral occipital gyri are shown). (B) Functional activation associated with correct inhibitions for Fixed (blue) and Random (red) SART. Correct inhibitions to unpredictable NOGO events in the Random SART activated right ventral frontal cortex, right inferior parietal cortex and left dorsolateral prefrontal cortex. Correct inhibitions to predictable NOGO events in the Fixed SART activated left middle frontal gyrus, left inferior frontal gyrus and left insula. (C) Functional activation associated with errors of commission collapsed across the Fixed and Random SART conditions. Areas shown include the anterior and posterior cingulate, left inferior frontal gyrus extending into insula, left inferior parietal lobe and left middle temporal gyri.

Table 2
Event-related activations for Fixed and Random SART

	Brodmann area	Hemisphere	Volume (μl)	Talairach coordinates (centre of mass)		
				x (RL)	y (AP)	z (IS)
<i>Activations for correct inhibitions</i>						
Frontal lobes						
IFG	45/47	L ^b	340	-52	16	3
IFG/MFG	47/10	R ^a	131	35	49	2
MFG	9	L ^a	136	-42	24	35
Premotor cortex	6	L ^b	162	-39	8	42
Parietal lobes						
Inferior parietal lobule	40	R ^a	244	36	-48	44
Angular gyrus	39	R ^b	264	44	-61	31
Postcentral gyrus/insula	40	L ^b	253	-47	-23	18
Subcortical regions						
Putamen/internal capsule		L ^a	193	-22	11	8
<i>Activations for commission errors</i>						
Frontal lobes						
Anterior cingulate	32	B	1231	1	25	28
IFG/insula	24/32	R	277	9	35	12
	47/45	L	1883	-45	19	1
	47	R	285	33	16	-9
	47	R	248	46	16	-1
MFG	9	L	153	-31	20	34
Temporal lobes						
Superior temporal gyrus	22	L	202	-62	-40	9
Parietal lobes						
Supramarginal gyrus	40	R	1778	47	-43	34
Inferior parietal lobule	40	L	174	-53	-44	26
	40	L	141	-64	-38	27
Subcortical regions						
Cingulate	23	L	847	-3	-23	28
Caudate		R	131	30	-40	12

Note: abbreviations are the same as for Table 1.

^a Signifies that activation was significantly greater in the Random than the Fixed SART.

^b Signifies that activation was significantly greater in the Fixed than the Random SART.

4.5. Relationship between tonic and phasic activation

We were interested in the interactions between tonic and phasic activation levels and, particularly between areas that might reflect the dynamic between the maintenance of task set information and levels of response conflict. The tonically activated left DLPFC region is a probable area for subserving the task set maintenance role [9,29,31,75] while the activated midline areas, particularly the ACC and pre-SMA, were likely to have subserved the conflict-monitoring role [15,78]. Mean activations associated with the Random SART in the following regions were correlated with each other treating subjects as a random effect; the left DLPFC

area [precentral gyrus (BA6) extending over the precentral sulcus onto the middle frontal gyrus (BA9)(centre of mass: $x = -43$, $y = 0$, $z = 32$)] and the pre-SMA region (-2 , -1 , 49) were both defined by the tonic OR map and the combined error map defined all three ACC regions (1,25,28; 9,35,12; -3 , -23 ,28). Only activations in the Random SART were examined, due to the small number of errors in the Fixed SART. A tight coupling was observed between left DLPFC and pre-SMA. Tonic left DLPFC activation correlated positively with tonic pre-SMA activation [$r(18) = 0.7$, $p \leq 0.001$]. This coupling was also present when examining phasic activity in these tonically defined ROIs. Hence, for errors of commission, phasic left DLPFC activity correlated with the same pre-SMA region [$r(18) = 0.65$, $p \leq 0.004$]. An inverse relationship between these two areas was observed in just one circumstance: Tonic left DLPFC activation correlated negatively with phasic pre-SMA activation for commission errors [$r(18) = -0.55$, $p \leq 0.02$]. Conversely, neither error-related nor tonic activation in the ACC regions correlated with error-related or tonic activity in the DLPFC or the pre-SMA. Neither were any of these correlations seen between midline areas and the right PFC ROIs.

5. Discussion

5.1. Neural network underlying response inhibition

Two separate networks were activated for correct inhibitions in the Fixed and Random SART. The distinctiveness of these networks was reflected in different patterns of response times for the Random and Fixed SART. Commission errors in the Random SART were significantly faster than GO response times, a common reaction time finding in GO/NOGO tasks suggestive of insufficient time to inhibit the prepotent GO response [47]. Conversely, NOGO error response times in the Fixed SART were not significantly different than GO response times, suggesting that errors may have been due to an inattentive default GO response. Therefore, the network of brain regions activated for Random correct inhibitions might be interpreted as being specifically related to response inhibition.

Correct inhibitions to unpredictable NOGO events in the Random SART activated the right ventral PFC, right IPL, left putamen and the left DLPFC. The involvement of prefrontal and parietal areas in response inhibition is very well established [10,30,41,45,46]. A role in inhibitory processes has been attributed to the right IPL based on GO/NOGO [30,54,67] tasks, Stroop tasks [62], Stop paradigm tasks [67] and the Simon task [62]. Ventral prefrontal involvement in inhibition has also been observed [30,38]. Konishi et al. noted right inferior frontal involvement in inhibition irrespective of which hand was used to respond in a GO/NOGO task [45] and across different types of inhibitory tasks [46]. Menon et al. [54] also found bilateral, but in

particular, right hemisphere activation of the inferior frontal sulcus for inhibitory events.

One discrepancy between this task and others that have attempted to measure response inhibition is our finding of left vs. right DLPFC involvement in response inhibition [11,30,54]. One reason for this disparity may be the relatively high verbal demands of the present task. Left DLPFC has been implicated in verbal working memory with a proactive interference component [39]. In a further experiment, D'Esposito et al. [24] found activation in this region during presentation of the probe when it must be compared to the “mnemonic representations of the memory set” (p. 7518). It may be that a similar process takes place in this experiment upon introduction of the NOGO stimulus in that there may be an internal check as to whether the number is part of the GO or NOGO set. Thompson-Schill et al. [76,77] have associated left inferior prefrontal cortex with selection of semantic knowledge in the face of distraction. However, the present GO/NOGO task had a much lower semantic demand requiring the inhibition of a prepotent response tendency and not selection between a number of semantic options.

Another possibility is that observed differences may be due to the use of a consistent stimulus–response mapping in this experiment (i.e., subjects always inhibited to the number 3), whereas others [11,30,31] have utilized variable stimulus–response mappings (that is, the appropriate response must be chosen for different contexts as it is not unambiguously determined by the stimulus). Variable mapping between the stimulus and the appropriate response may require response selection in which participants must select whether a particular stimulus represents a GO or a NOGO response. This function has been attributed to right DLPFC [31,66] and this may explain why this area was not observed for the consistent mapping inhibition of the present study. If the stimulus–response mappings are variable, mappings need to be maintained in working memory, and there may be increased demand on selecting the appropriate mapping. Consequently, it may follow that right frontal activations may not be associated with inhibition, per se, but with additional processes required at the time of inhibition. Consistent with this reasoning, a recent study [57] has suggested that right prefrontal involvement may be attributable to task complexities, which require additional processes such as working memory at the point of inhibition. The authors in this study found activation in the pre-SMA alone when a very simple GO/NOGO task was employed but found additional DLPFC activation as task complexity was increased.

In contrast, a mainly left-lateralized network of areas was observed for correct inhibitions to predictable NOGO events in the Fixed SART. Left DLPFC was activated during Fixed correct inhibitions and has previously been implicated in task set maintenance [29,31,50,68]. A similar area was also activated tonically in the Fixed and Random SART. It may be that this region is involved in tonic task set maintenance

and also reactivates task set just prior to or during the occurrence of the predictable number 3 in the Fixed SART. Consistent with this functional attribution, Brass and von Cramon [9] have recently shown this area to be active during task preparation.

5.2. Tonicly activated executive functions

An extensive, task-related, tonic activation pattern was observed including visual and motor areas. Of particular interest, however, are those areas that may be associated with executive processing. As mentioned, one particular area of note, the left DLPFC, has previously been implicated in maintenance of representations [29,50,68]. This same area was observed in a GO/NOGO study after subjects adjusted their behavior following commission errors and was interpreted as being involved in maintaining/reestablishing task set [31]. Consequently, this left DLPFC area, which was significantly active for both the Fixed and the Random SART, as well as for Fixed correct inhibitions, was likely to have been involved in the maintenance of the task set or goals.

The pre-SMA region was seen to be significantly more active for the Random over the Fixed SART. Given this region's involvement in motor preparation [63,74], it may be that the increased need for motor preparation in the Random SART, i.e., the need to be primed to withhold a response, may be responsible for this activation pattern. Another possibility is that the pre-SMA is monitoring for response conflict. This region and more inferior midline regions within the ACC have been implicated in conflict monitoring [10,11,15,78] and it is reasonable to assume that the Random SART would generate greater amounts of tonic response conflict than the Fixed SART. This latter interpretation is consistent with the pattern of correlations, discussed below, between the left DLPFC and the pre-SMA. Furthermore, if response conflict were generated by the coactivation of competing motor responses then a role for this structure in conflict monitoring would be consistent with its role in motor preparation [32].

Finally, right parietal and prefrontal areas were anticipated to be tonically active given their established role in sustained attention [20,21,71,84]. An unexpected but significant deactivation was seen in the right SPL for the Fixed SART and activation was observed in the left IPL and bilateral superior lobules (extending into the IPL in the right hemisphere) and the right IFG in both conditions. Manly et al. [52] found activation in the right DLPFC and right parietal cortex for the Fixed over the Random SART in their PET study, whereas we did not find any activation for the Fixed over the Random SART. The use of a relatively quiet PET environment, an older subject group (mean of 51.9 vs. a mean of 26.4 in this study), unvarying stimulus presentation and the absence of a response cue in their study may have been more sensitive than ours to detecting endogenously driven attention.

5.3. Conflict monitoring and error processing

Some controversy exists as to whether the ACC is involved in error processing per se or rather conflict monitoring [15,42,68,78]. Carter et al. [15] observed activation in the ACC not only during error trials but also during trials involving high amounts of response conflict. Other evidence suggests that the more rostral region of the ACC may be involved in error detection and the more caudal ACC extending into the pre-SMA may be involved in response conflict [10,60,78,80]. In the present study, a widespread pattern of activity was observed for Fixed and Random errors. These included two regions in the ACC and two left inferior parietal regions. The medial parietal lobes (precuneus) have previously been implicated in error processing [54] and the left parietal lobe has also been considered to be a contributor to the P_E (error positivity) [81], a component of error trial ERPs that is thought to reflect error processing. These ACC regions were not activated tonically during task performance. Conversely, an area in the pre-SMA displayed significantly greater tonic activation for the Random SART but did not show a phasic error-related response. Together, these findings suggest that the more rostral area of the ACC is an error processing area and that the more caudal ACC area extending into the pre-SMA serves a response conflict-monitoring function [10,42,54,78].

5.4. PFC and midline interactions

Barch et al. [4] predicted a correlation between DLPFC and ACC, under the assumption that conflict monitored by the ACC would trigger recruitment of top-down attentional resources from the DLPFC. In the present study, this relationship was seen between DLPFC and pre-SMA. A positive correlation was also seen between phasic activation of left DLPFC and phasic pre-SMA for errors of commission. We would expect to see this pattern if cognitive control were effected by the detection of high levels of conflict by pre-SMA triggering a rise in top-down control exercised by left DLPFC akin to the model suggested by Botvinick et al. [8]. In effect, those subjects who showed the greatest midline (response conflict) activation also showed the greatest left DLPFC (top-down control) activation. Consistent with this interpretation, individuals who displayed low tonic levels of top-down control showed increased levels of phasic conflict, monitored by pre-SMA, on error trials. This relationship also supports existing models [7,10,15] which posit that cognitive control is achieved by the PFC maintaining representations of task-relevant information and suppressing competing or distracting, task-irrelevant information, thus reducing response conflict as monitored by the ACC, or as in this task, the more caudal part of the ACC extending into the pre-SMA region. Together, these correlations add strong support to the concept of a reciprocal relationship between these two regions [19], the pre-SMA

monitoring for conflict and feeding back to DLPFC, which maintains task set and allocates attentional resources.

Interestingly, the interregional correlations that have been reported above were not seen between DLPFC and ACC. That this relationship was not observed suggests that the ACC activation observed during error trials may not reflect a conflict-related activation. Instead, one conjecture, in need of further corroborating evidence, is that the ACC activation may reflect emotional [13,48,49,54], reward-related processes [27,33,35,68] or may be monitoring performance in some other way. In fact, in a recent review paper, Schall et al. [70] have illustrated that, in monkeys, there has been no evidence of conflict-related neural activity in ACC whereas they have seen clear examples of this in pre-SMA. A recent electrophysiological study attempted to dissociate conflict-related processes and error monitoring in a neurological patient with a lesion of rostral ACC extending into dorsal ACC [72]. The patient displayed a reduction in ERN compared to controls and also displayed lower error correction rates. However, the stimulus-locked N450 component that was interpreted as reflecting response conflict processes was enhanced. This is suggestive of a dissociation of error- and conflict-related processes along the midline, with the intact pre-SMA possibly monitoring for response conflict. Finally, Ullsperger and von Cramon [79] provided more evidence of pre-SMA involvement in conflict monitoring in their imaging study of error monitoring using external feedback. In a task in which subjects were highly uncertain about the outcomes of their actions, the authors provided positive, negative and neutral feedback. They postulated that conflict-related activity should occur on high-conflict trials irrespective of the type of feedback that was provided (noninformative or negative), whereas activity related to negative feedback should occur only after trials in which participants were provided with informative feedback. They report that the rostral cingulate motor area was activated by negative feedback, whereas pre-SMA responded to response conflict. The fact that we found no relationship between ACC and left PFC whereas we did between pre-SMA and PFC is an interesting finding with regard to the ongoing debate as to whether errors themselves or simply levels of response conflict trigger additional recruitment of top-down control as enforced by PFC. In this particular experiment, it appears that error-related activity detected by ACC does not directly engage PFC as we found no correlation between these two areas, even during errors. Perhaps, this suggests that the characteristic finding of posterror behavioral adjustment [64] can be explained by high levels of conflict-related activity during errors triggering PFC involvement as has been previously suggested by Botvinick et al. [8].

6. Conclusion

In summary, the comparison of correct inhibitions to unpredictable NOGO events with inhibitions to predictable

NOGO events revealed a discrete number of prefrontal and parietal brain regions implicated in inhibitory control. The rostral area of the ACC and the left parietal lobe displayed a role in error processing, whereas the more dorsal part of the ACC and the pre-SMA appeared to play a role in conflict monitoring. Guided by previous research, we suggest that the parietal and right prefrontal areas were involved in sustained attention while the left DLPFC actively maintained the task set. These results reveal a neuroanatomical fractionation of those executive functions critical for smooth behavioral control. Furthermore, the interregional correlations revealed that midline regions and DLPFC work cooperatively in order to complete the task successfully, constantly working in parallel to monitor conflict, maintain task goals and enforce control.

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