

Beyond common resources: the cortical basis for resolving task interference

Robert Hester,^a Kevin Murphy,^a and Hugh Garavan^{a,b,*}

^aDepartment of Psychology and Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland

^bDepartment of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, USA

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Recent studies have suggested that declining inhibitory control observed during simultaneous increases in working memory (WM) demands may be due to sharing common neural resources, although it is relatively unclear how these processes are successfully combined at a neural level. Event-related functional MRI was used to examine task performance that required inhibition of varying numbers of items held in WM. Common activation regions for WM and inhibition were observed and this functional overlap may constitute the cortical basis for task interference. However, maintaining successful inhibitory control under increasing WM demands tended not to increase activation in these overlapping regions as might be expected if these common areas reflect common resources essential for task performance. Instead, increased activation was observed predominantly in unique, inhibition-specific regions including dorsolateral prefrontal cortex. The finding that successfully maintaining weaker stimulus–response relationships in the face of competition from stronger, prepotent responses requires greater activity in these regions reveals the means by which the brain resolves task interference and supports theories of how top-down attentional control is implemented.

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Introduction

Kane, Engle, et al. (Engle et al., 1999; Kane and Engle, 2003; Kane et al., 2001) argue that the ability to control attention underlies the ability to inhibit irrelevant processing and to switch between competing tasks. This theory developed on some earlier work (Hasher and Zacks, 1988), including other models of attention that had also grouped these functions, for example, Baddeley (2001), attributes them to the central executive component of his tripartite WM model and Burgess and Shallice (1998) to their supervisory attentional system. Within

these models is the suggestion that the ability to control attention is influenced by and related to working memory (WM). For instance, Kane et al. argue that controlling attention is, among a number of things, the ability to maintain a stimulus or goal in the face of interference. As such, WM capacity provides an index of this ability due to the requirement of many WM tasks to simultaneously store and process information in the face of interference.

Kane et al., along with other groups, have demonstrated a relationship between an individual's ability to perform traditional executive tasks such as the Stroop (Kane and Engle, 2003) and antisaccade task (Kane et al., 2001) and their WM capacity (Baddeley et al., 2001; de Fockert et al., 2001; de Zubicaray et al., 2000; Mitchell et al., 2002; Roberts et al., 1994). For example, Roberts et al. (1994) demonstrated that antisaccade task performance declined as WM demands were increased. de Fockert et al. (2001) were able to demonstrate that with increasing WM demands, processing of irrelevant face information, measured via functional MRI, increased activity in the extrastriate and fusiform cortex. The suggestion from these studies is that WM plays a critical role in actively maintaining attentional priorities. As a consequence, when greater load demands are placed on WM, implementing these 'attentional priorities' suffers, and greater processing of irrelevant information occurs.

Imaging studies have implicated the dorsolateral prefrontal cortex (DLPFC) in a number of roles important to both WM and the attentional control required for inhibition. For example, many studies examining executive function tests such as the Stroop, Eriksen Flanker, and Go/No-go tasks have identified this region, arguing that the DLPFC is crucial to the performance of executive tasks where a set of task rules must be maintained in the face of irrelevant information (MacDonald et al., 2000; Ullsperger and von Cramon, 2001; Zysset et al., 2001). A large body of research has also suggested that when required to maintain increasing WM loads, the level of activation in the DLPFC selectively increases (Braver and Bongiolatti, 2002; D'Esposito et al., 1999; Rypma et al., 2002; Veltman et al., 2003). Similarly, Rowe et al. (Rowe and Passingham, 2001; Rowe et al., 2000) argue that selecting a response from WM is associated with activation of the DLPFC, in particular Brodmann's area 46.

* Corresponding author. Department of Psychology and Trinity College Institute of Neuroscience, College Green, Trinity College, Dublin, Dublin 2, Ireland. Fax: +353-1-671-2006.

E-mail address: hugh.garavan@tcd.ie (H. Garavan).

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A conclusion drawn from this research is that perhaps WM and inhibitory control depend on common neural circuitry, particularly in regard to the PFC. Bunge et al. (2001) examined this very question by looking at the effect of manipulating the level of proactive interference within a Sternberg-type WM task. They found that both increasing WM load (one to six items) and the interference manipulation resulted in activation of similar cortical networks, overlapping in key regions including the lateral prefrontal cortex (both dorsal and ventral), insula, anterior cingulate (ACC), and parietal cortex. Bunge et al. (2001) argued that the PFC's part in the common circuitry was consistent with theoretical models (Cohen et al., 1996; Kimberg and Farah, 1993; Miller and Cohen, 2001), suggesting that it has a dual role in WM and behavioral inhibition. Bunge et al. (2001) also suggested, in accordance with this modeling, that increasing WM load in a task such as de Fockert et al.'s (2001) indicates "that when PFC is otherwise occupied (with WM), behavioral interference susceptibility and brain activation related to the processing of irrelevant stimuli are both increased" (p. 2084).

The neuroimaging literature appears to provide support for the assertion that the decline in inhibitory control resulting from a simultaneous increase in WM load is due to sharing a common neural network. This presents an interesting question: How does this common network, or the brain in general, cope with exerting inhibitory control as the items currently being rehearsed in WM increases? While behavioral studies show a decline in performance, this decline is far from catastrophic with people remaining able to exert a high level of inhibitory control under duress from greater WM demands. The main aim of the current study is to elucidate the neural mechanics underlying the maintenance of performance under such competing demands. While the notion of 'common resources' has been proposed to explain why there is interference between competing tasks, it remains unclear how these common cortical regions, and for that matter the rest of the brain, compensates or copes with the dilemma of having two different simultaneous demands on the same part of the brain.

To test this question, we designed a task that integrated the requirement to actively maintain items in WM during the exertion of inhibitory Go/No-go performance. The advantage of this design is that participants cannot strategically switch between the two tasks in an attempt to improve performance, rather they are required to use the contents of WM in order to successfully exert inhibitory control. Also, it provides a more explicit and potentially more challenging manipulation of competing inhibitory and WM demands, as for example, Bunge et al. (2001) were unable to demonstrate performance accuracy declines, or awareness of proactive interference, resulting from the manipulation in their task. This aspect of the design allows us, with event-related functional MRI, to examine activation during the successful inhibitory events and determine whether the network of regions activated by maintaining items in WM, and inhibitory control, are common or distinct. By linking WM processing and inhibition, in that the maintenance of a WM load is intimately related to both the WM and inhibitory requirements of the task, we can explore how the brain copes with multiple cognitive demands without being able to strategically switch between them. The event-related approach also provides an opportunity to examine how the brain successfully resolves the dilemma of competing cognitive demands on common cortical regions when maintaining cognitive control.

Successfully withholding a response to the No-go trials is argued to represent inhibitory control over a prepotent response, typically resulting in activation of prefrontal, parietal (predominantly right hemisphere), and midline (ACC and pre-SMA) regions (de Zubicaray et al., 2000; Garavan et al., 2002; Konishi et al., 1999; Liddle et al., 2001; Rubia et al., 2003; Watanabe et al., 2002). In line with previous behavioral studies, we predicted that increasing WM load would negatively influence inhibitory performance; however, it was unclear from previous literature what influence WM load would have on this event-related inhibitory activation response. The current design examined this using a parametric manipulation of WM load during inhibitory events. The task therefore represented a test of the 'common neural circuitry' hypothesis for WM and inhibition, but also further explored how this network, and the rest of the brain copes with increasing WM demands during inhibition.

Methods

Subjects

Fifteen right-handed subjects (8 female, mean age 31, range: 20–40), reporting no history of neurological or psychological impairment, were recruited from the volunteer subject pool of the Medical College of Wisconsin. All subjects provided informed consent.

Behavioral task

Subjects completed a Go/No-go inhibition task based on our earlier work (Hester and Garavan, *in press*). The Working Memory Load Inhibitory Task (WMLIT) presented a primary inhibitory task, within which a working memory load was embedded (see Fig. 1). To begin the task, subjects were shown a 'memory list' of 1, 3, or 5 uppercase letters. The memory list was presented for 6 s and immediately followed by a rehearsal period of 8 s that presented a white crosshair on a black background. Participants were instructed during the practice session to use this 8 s period for rehearsal of the items. A series of 60 decision trials then followed, each lasting 1500 ms, including the presentation of a single letter in white font on a black background for 1000 ms, and a blank screen for the concluding 500 ms. The participant was instructed to respond as quickly as possible and decide whether the letter was part of the memory list or not. The participant was trained to press a button for each trial featuring a letter that was not part of the memory list (Go trials) and withhold their response for items that were part of the memory list (No-go trials). The 60 trials included 53 Go trials and 7 No-go trials, which were pseudorandomly placed throughout each run. The purpose of the unequal distribution was to create a prepotent response for the Go trials, in that the participant would become accustomed to pressing the button for each trial and be required to suppress the prepotent response in order to successfully withhold to No-go trials.

Each participant received 18 experimental runs, with 6 runs per memory list size (1, 3, or 5 items) and a single run composed the 6-s encoding period (encoding), 8-s rehearsal period (rehearsal), 60 consecutive 1.5-s decision trials (trial period), and a 30-s concluding rest interval (rest). The order of runs was identical for each participant, with the sequence of presentation counterbalancing

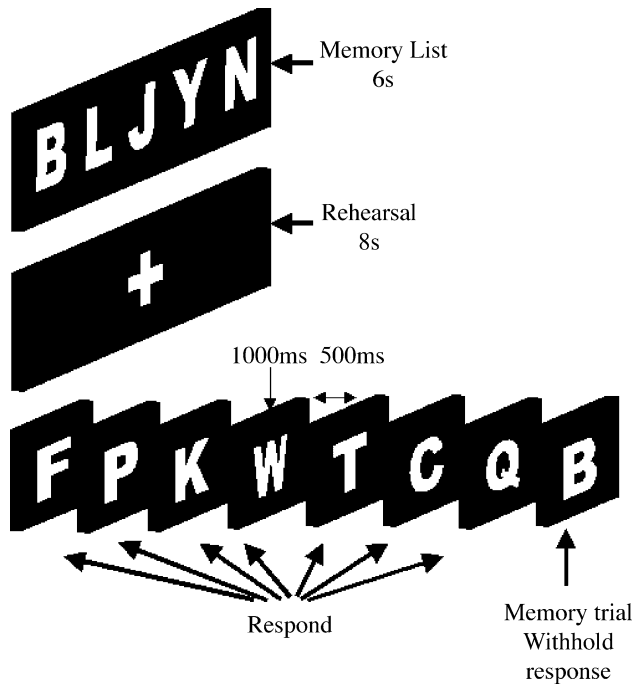


Fig. 1. Working memory load inhibition task design. The design of the task requires participants to withhold a prepotent response to an increasing number of items currently held in WM. At the beginning of the task, a memory list of 1, 3, or 5 items was presented. A series of single letters were then presented to which participants were told to press a button if the item had not been part of the memory list (88% of trials) and withhold their response if it had.

memory load requirements (i.e., 1, 3, 5, 3, 5, 1, 5, 3, 1, etc.). At the conclusion of every third run, a longer (unscanned) rest period was provided.

During the practice administration of the task, the final trial of a run was followed by asking participants to recall the letters from the current memory list by typing them on the keyboard. No time limit was imposed for this recall period and letters could be typed in any order. Due to practicalities of MRI administration, this aspect of the task was not administered during the scanner runs; however, the practice administration revealed recall of over 98% for the most difficult memory load (load 5), which is in accordance with three previous administrations of the task (Hester and Garavan, *in press*). This, along with subjects' self-reports, suggests that commission errors during the task were not due to forgetting the memory items.

Scanning parameters

Scanning was conducted on contiguous 7-mm sagittal slices covering the entire brain from a 1.5-T GE Signa scanner 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). High resolution spoiled GRASS anatomic images (TR = 24 ms, TE = 5 ms, flip angle = 45° , FOV = 24 cm, thickness = 1.0 mm with no gap) were acquired following the functional imaging to allow subsequent activation localization and for 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. The

task was programmed and displayed using E-prime (v.1, Psychology Software Tools, Pittsburgh, PA, USA).

All analyses were conducted using AFNI software (Cox, 1996). Following image reconstruction, the time series data were time shifted using Fourier interpolation to remove differences in slice acquisition times and motion corrected using 3D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was also removed using edge detection techniques. No subjects showed significant residual motion; thus, allowing all 15 to be included. Although the stimulus stream was presented at 1.5 Hz, all events of interest were time locked to the beginning of the 2-s whole brain volume acquisition during presentation of the task.

Comparisons of interest

To examine the influence of WM demands on inhibitory control, an event-related analysis was performed that estimated the activation separately for inhibitions during each of the WM load conditions. To do this, separate hemodynamic response functions at 2 s temporal resolution were calculated using deconvolution techniques for successful response inhibitions (Stops) at each load size (designated Stops 1, 3, and 5). Due to the relatively small number of error events, the deconvolved hemodynamic response for errors of commission (errors) included the errors committed over all load sizes. A nonlinear regression program determined the best-fitting gamma-variate function for these IRFs (Cohen, 1997) as previously described (Garavan et al., 1999). The area under the curve of the gamma-variate function was expressed as a percentage of the area under the baseline. The baseline for this task was the ongoing trial period (Go trials) activity for that load size, with the activation for other parts of the task (i.e., encoding, rehearsal, and rest) censored from the analysis. Therefore, the activation observed during these events represents the activation for the events over and above that required for the ongoing trial period (or Go) responses.

The separate activation maps were then combined, deriving an OR map of Stops that included all voxels of activation indicated as significant from any of the constituent maps (Stops 1, 3, or 5). The mean activation for clusters in the OR map was calculated for the purposes of an ROI analysis, and these data were used for a repeated measures comparison between load size conditions, corrected using a modified Bonferroni procedure for multiple comparisons (Keppel, 1991).

To examine common and distinct regions of activation for both WM and inhibition, the results of the aforementioned event-related analysis were combined with a block analysis. The block analysis derived separate hemodynamic block activation functions for the WM processes of encoding and rehearsal, calculated for each memory load size and representing the averaging of signal across runs of the same load size. A regression analysis was used whereby activation for the encoding and rehearsal blocks was calculated as a percentage change relative to baseline. The baseline in this analysis was the 30-s rest periods following the cessation of each run.

The percentage area (event-related activation) and percentage change map (block activation) voxels were resampled at 1 mm^3 resolution, then warped into standard Talairach space (Talairach and Tournoux, 1988), and spatially blurred with a 3-mm isotropic rms Gaussian kernel. Group activation maps for each load size (Stops, encoding, and rehearsal) were determined with one-sample *t* tests against the null hypothesis of zero event-related activation

changes (i.e., no change relative to baseline). Significant voxels passed a voxelwise statistical threshold ($t = 5.226$, $P = 0.0001$) and were required to be part of a larger 78 μl cluster of contiguous significant voxels. Thresholding was determined through Monte Carlo simulations and resulted in a 1% probability of a cluster surviving due to chance.

To observe the common regions of activation for WM and inhibition an AND map was formed, combining the Stops and rehearsal OR maps. An AND map includes the voxels of activation indicated as significant from both of the constituent maps. An AND map was also formed for the regions of common activation between the encoding and rehearsal blocks.

Results

Behavioral performance

Table 1 demonstrates the negative influence of WM load on Stops and Go trial RT. Increasing memory load significantly reduced the number of Stops, $F(2,28) = 20.05$, $P < 0.0001$, with pairwise comparisons confirming significant differences between performance at all three load levels (1 vs. 3, 1 vs. 5, 3 vs. 5). A similar result was also evident for Go RT, indicating significantly slower Go RT with increasing WM load, $F(2,28) = 196.30$, $P < 0.0001$, and pairwise comparisons again confirming significant differences between mean RT for each load size. The RT during error trials was compared with Go RT, indicating different results at the different load sizes. At the one-item load, error RT was significantly faster than Go RT (see Table 1), $t(14) = 4.04$, $P < 0.001$, typical of previous studies using one-item Go/No-go tasks (Menon et al., 2001). At the three-item load, error RT and Go RT were not significantly different, and at the five-item load, error RT was significantly slower than Go RT, $t(14) = -2.62$, $P < 0.05$.

Effect of working memory load on functional activation

Encoding

Of the regions of interest identified from the encoding OR map, seven demonstrated significantly greater activation with increased WM load in clusters critical to WM, including two clusters in the left DLPFC (BA 9 and BA 46) and one in the ACC (BA 32) (see Table 2). Four other clusters were sensitive to increasing WM load, the left fusiform and lingual gyri and right inferior occipital lobe and cerebellum.

Rehearsal

ROIs identified from the rehearsal OR map indicated significant WM load-related activation increases in bilateral middle frontal and inferior parietal lobule, as well as significant clusters in the cerebellum, right occipital, left fusiform, and pre-SMA regions (see

Table 1
Mean number of Stops (represented as a percentage of total No-go trials), Go reaction time (RT), and error RT for each memory load condition

	Stops		Go RT		Error RT	
	M	SD	M	SD	M	SD
Load 1	92.8	5.2	451.9	59.2	378.5	70.4
Load 3	86.5	9.2	544.6	59.5	547.8	96.4
Load 5	78.6	12.5	606.1	59.6	648.5	108.9

Table 2

Unique regions of activation sensitive to WM load during the encoding and rehearsal periods, as well as regions of common activation for the encoding and rehearsal periods

Structure	BA	HS	Vol (μl)	Centre of Mass		
				x	y	z
<i>Encoding</i>						
Frontal lobe						
Middle frontal	9	L	4550	-43	4	29
Middle frontal	46	L	212	-40	31	19
Anterior cingulate	32	L	441	-7	33	24
Temporal lobe						
Fusiform	37	L	379	-39	-52	-10
Occipital lobe						
Inferior	18	R	136	29	-82	-4
Lingual	17	L	320	-21	-92	-5
Cerebellum						
Anterior		L	167	29	-55	-24
<i>Rehearsal</i>						
Frontal lobe						
Middle frontal	9/46	R	237	38	31	26
Middle frontal	6	L	188	36	-55	40
Anterior cingulate	32	L	261	-3	18	42
Parietal lobe						
Supramarginal	40	L	418	-40	-42	36
Subcortical						
Lentiform or putamen		L	278	-21	8	2
Insula	13	R	239	35	17	1
<i>Common regions for both encoding and rehearsal</i>						
Frontal lobe						
Middle frontal	9	L	1411	-44	2	31
Middle frontal	46	L	95	-42	31	19
pre-SMA/ACC	6/32	L	1666	-2	12	48
Parietal lobe						
Inferior	7	R	576	30	-55	41
Superior	40	L	350	-40	-41	36

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

Table 2). Interestingly, the encoding and rehearsal maps had significant common activation in bilateral parietal, left DLPFC (both BA 9 and 46) and the pre-SMA/ACC region (see Table 2 and Fig. 2). No common activation was found in the right DLPFC.

Stops

Significant load-related activation was observed in only 9 of 36 regions defined by the Stops OR map. The regions included the right middle frontal gyrus (BA 9 and 6), left middle temporal gyrus (BA 20), left middle frontal gyrus (BA 6), and thalamus (see Table 3 for coordinates). The cingulate region also showed sensitivity to load, with significant activation increases in both rostral (BA 32/24) and dorsal ACC/pre-SMA (BA 32/6) (see Table 3). The cerebellum had two regions sensitive to load during Stops; however, the pattern was in the opposite direction with activation decreasing under greater WM demands (see also Fig. 3). No clusters in the parietal region were found to be sensitive to load.

To examine the brain-behavior relationship between activation levels and behavioral performance, a split-half comparison was performed dividing the sample on the basis of the number of correct inhibitions across the entire task into high and low performance groups. A 2 (group) \times 3 (load) ANOVA indicated

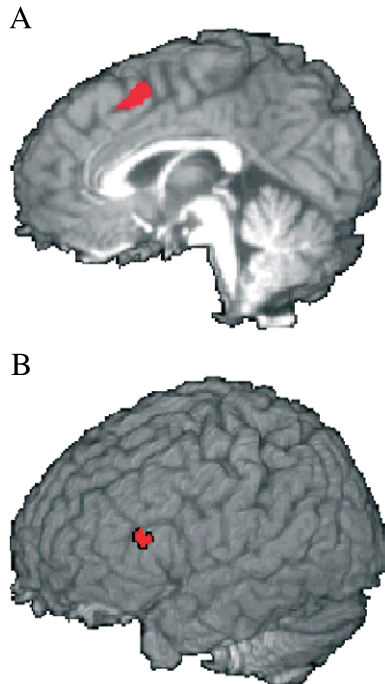


Fig. 2. Regions of activation common to both WM encoding and rehearsal: (A) dorsal ACC/pre-SMA region (BA 32/6), (B) left DLPFC (BA 46).

that the high performance group had significantly greater success at the task (89% vs. 79% correct inhibitions, $P < 0.01$) and also demonstrated significantly greater activation in three clusters: the right middle frontal gyrus (see Fig. 4A, blue and red clusters) and the dorsal ACC/pre-SMA region (see Fig. 4B, red cluster), all of which were identified as being sensitive to increasing WM load. A fourth activation cluster approached significance for group differences ($P < 0.06$), also in the right middle frontal gyrus (see Fig. 4A, orange cluster). No interaction was found between the group and load effects.

Common regions required for WM rehearsal and STOPS

The spatial overlap of regions active during the rehearsal period and Stop events indicated seven clusters of common activation, which are presented in Table 4 and Fig. 5. The regions included the right (BA 9) and left (BA 6) middle frontal gyrus, right and left inferior parietal lobule, ACC, right insula, and left putamen region. The response of these common activation regions to increasing WM load was also examined, indicating that during Stops, the ACC and left middle frontal gyrus showed significantly greater activation with increasing WM load. However, the insula, right middle frontal, and bilateral parietal regions did not show significant increases in activation with load. A 2 (performance group) \times 3 (load) ANOVA indicated that the high performance group had significantly greater activation in only the common dorsal ACC/pre-SMA region.

Discussion

The requirement to withhold a prepotent response to items held in WM resulted in poorer inhibitory control with greater WM demands. The manipulation of WM demand appeared

effective as significant activation increases were seen during the encoding and rehearsal phases of the task, with activation in bilateral parietal and middle frontal, left DLPFC (both BA 9 and 46), left fusiform, right occipital lobe, cerebellum, and the pre-SMA/ACC region. The pattern of neural activation seen for successful inhibition indicated bilateral middle frontal and parietal regions, midline (pre-SMA and ACC), temporal, subcortical, and cerebellar regions. Only a small selection of these regions showed sensitivity to WM demands, and fewer still demonstrated activation in common with WM rehearsal. Through the manipulation of WM demands, we were able to observe functional correlates in the common and unique WM and inhibition areas and these observations yield insights into the neural basis of the interactions between the two.

Table 3

Regions of event-related activation during successful response inhibition (Stops)

Structure	BA	HS	Volume (μ l)	Center of mass			P
				x	y	z	
Frontal lobe							
Superior frontal	10	R	889	25	48	26	
	9	L	426	-30	38	30	
Middle frontal	9/6	R	597	40	4	38	*
	10	R	1268	37	37	19	
	10	L	111	-38	47	14	
	9	R	198	38	18	38	*
Precentral	6	R	2902	18	4	55	
	6	L	576	-24	-2	54	
	6	L	159	-38	1	43	*
	6	L	152	-38	1	28	
Pre-SMA/ACC	6/32	L	1074	-5	14	46	*
Anterior cingulate	32/24	L	1325	-2	33	22	*
Parietal lobe							
Inferior parietal	40	R	6230	38	-44	38	
	40	L	2207	-39	-46	39	
	40	L	114	-52	-46	28	
Precuneus	7	L	335	-23	-67	39	
Cingulate	23	L	139	-3	-13	26	
	31	R	117	8	-43	40	
Temporal lobe							
Superior temporal	39	L	343	-52	-54	10	
	39	R	118	50	-48	10	
Middle temporal	21	R	423	55	-33	-5	
	20	L	166	-50	-32	-9	
	21	R	113	53	-46	-4	
Fusiform	37	L	205	-32	-51	-8	
Subcortical							
Thalamus		B	574	-1	-15	-1	*
		B	377	17	-14	17	
Lentiform		R	5753	22	8	5	
		L	1182	-21	8	2	
Caudate		R	173	13	10	12	
		L	285	-14	1	12	
Cerebellum							
Culmen		L	1775	-33	-49	-25	*
		L	268	-18	-62	-43	*
Inferior		L	186	-12	-68	-25	
		R	160	13	-61	-32	
	R	141	33	-54	-23		

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

*Represents clusters found to be sensitive to increasing WM load ($P < 0.05$, corrected).

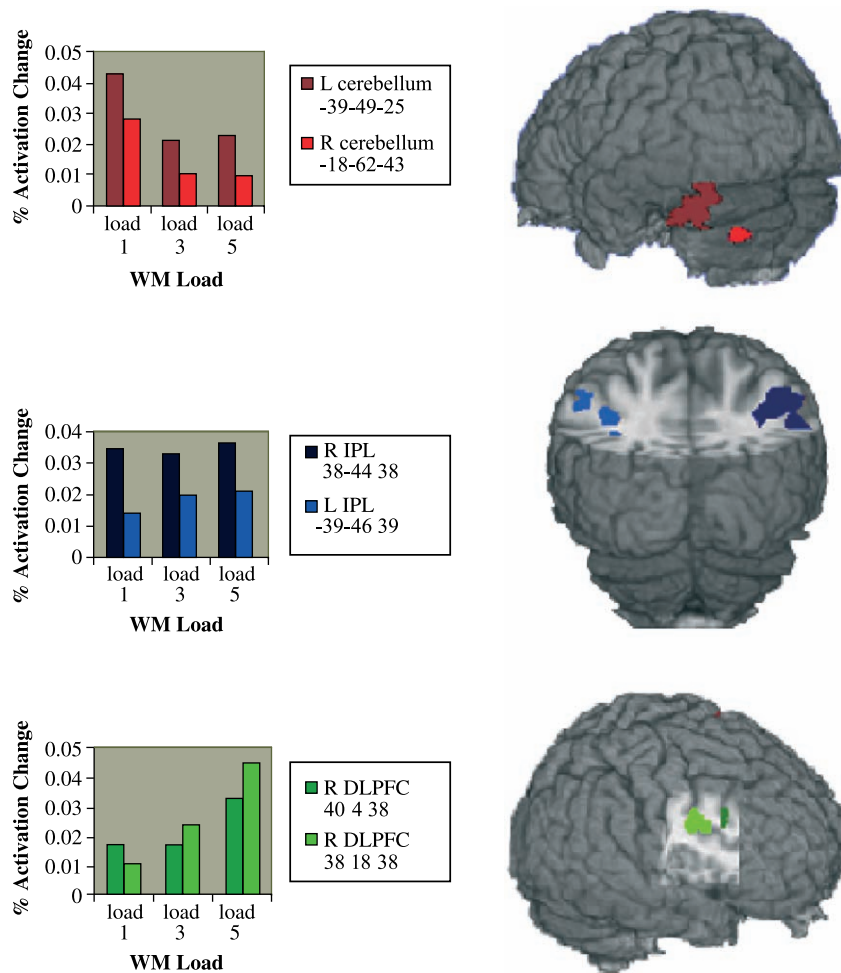


Fig. 3. Sensitivity to WM demands of the DLPFC, parietal lobe, and cerebellum during Stops.

Interactions between working memory and inhibition

The results of the present study indicate, in line with previous behavioral studies, that increasing working memory demands negatively influenced inhibitory control (de Fockert et al., 2001; Kane and Engle, 2003; Kane et al., 2001; Mitchell et al., 2002; Roberts et al., 1994). Despite a decline in performance, participants were able to successfully inhibit a prepotent response on the majority of No-go trials, and during these inhibitions activation was seen in prefrontal, parietal (predominantly right hemisphere), midline (ACC and pre-SMA), and subcortical regions, consistent with the findings of previous Go/No-go tasks (de Zubicaray et al., 2000; Garavan et al., 2002; Konishi et al., 1999; Liddle et al., 2001; Rubia et al., 2003; Watanabe et al., 2002). Given this performance, we examined further how this network of regions successfully responded to increasing WM demand. Seven clusters were sensitive to this manipulation, including both rostral and dorsal ACC/pre-SMA, right DLPFC (two clusters in BA 9 and 9/6), left prefrontal, left temporal, and thalamus. Of these regions, both the pre-SMA and right DLPFC also demonstrated a brain–behavior relationship, with greater activation predicting better inhibitory performance. Mostofsky et al. (2003) recently found greater right DLPFC activation during a Go/No-go task that made inhibition dependent on counting

variable numbers of stimuli, with the suggestion that this placed greater demands on WM.

In the following sections, we will discuss the implications of these findings for theories of prefrontal function, overlap in cognitive or neural resources, and the specific roles of different brain regions.

Common resources

One hypothesis to explain the greater difficulty of exerting inhibitory control under increasing WM demands is the strain placed on a common neural network. This hypothesis appears to argue that cognitive processes that share brain loci also share resources. This suggestion may not necessarily be true, for example, there is evidence from single cell research that cells in the same region can have different functions, and might therefore represent intermingled yet distinct resources (Hanes et al., 1998; Requin et al., 1988). However, consistent with the findings from Bunge et al. (2001), WM rehearsal and inhibitory control showed common activation in bilateral prefrontal and inferior parietal regions, as well as the ACC, right insula, and left putamen. Examination of this common network during inhibitory control indicated that the dorsal ACC and left prefrontal region showed increased activity with increasing WM demands and that the

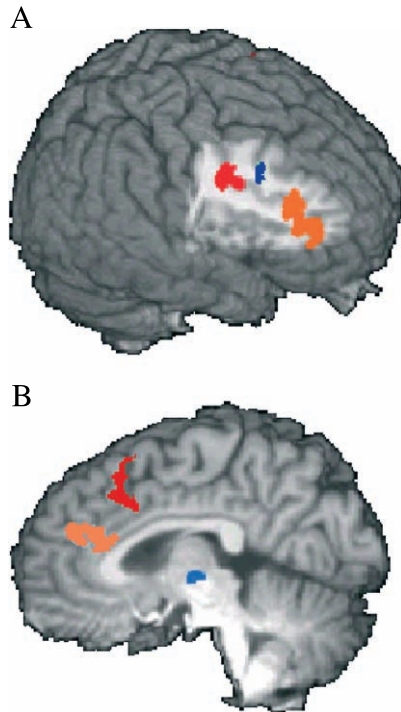


Fig. 4. Regions of event-related activation during successful response inhibition (Stops) sensitive to increasing WM demands: (A) orange—right DLPFC (BA 10/46), blue—right DLPFC (BA 9), red—right DLPFC (BA 9/6); (B) orange—ACC (BA 32/24), red—pre-SMA (BA 6/32), blue—thalamus.

increased activation in the ACC was associated with improved inhibition performance.

These findings provide support for the hypothesis of Bunge et al. (2001) that placing competing cognitive demands on common cortical regions results in interference on task performance. For example, the common load-sensitive region in the left prefrontal cortex has been implicated in both the maintenance of task goals during executive function tasks (MacDonald et al., 2000; Ullsperger and von Cramon, 2001) and WM rehearsal (Curtis and D’Esposito, 2003; D’Esposito et al., 1999; Rypma et al., 2002). Similarly, the dorsal ACC/pre-SMA region found to be common to both tasks has been widely identified across a range of tasks (Duncan and Owen, 2000), including inhibitory control (Garavan

et al., 1999; Rubia et al., 2003) and WM (Kondo et al., 2004; Nyberg et al., 2003; Osaka et al., 2003). The finding that individual differences in this particular cingulate response were predictive of performance highlights it as a region critical to maintaining successful performance, though it is unclear what precise role the cingulate might be playing. Several different proposals for the cingulate’s role in higher cognition have been put forward, including attentional control (Posner and Rothbart, 1998), increased effort (Dehaene et al., 1998), monitoring of conflict or competition (Botvinick et al., 2001; Carter et al., 1999), and response monitoring (Garavan et al., 2003; Ullsperger and von Cramon, 2001, 2003), all of which are potentially consistent with the role it may be playing in the current task.

While it appears that placing greater demands on common resources provides an explanation for performance decline, we were primarily interested in how the brain is able to maintain performance in spite of these competing demands. Increasing activation in the common dorsal ACC/pre-SMA region appeared to be one element of how this was achieved. However, individual differences in the ability to increase activity in the right DLPFC was another significant predictor of performance. The clusters of activation predictive of performance in this region were seemingly

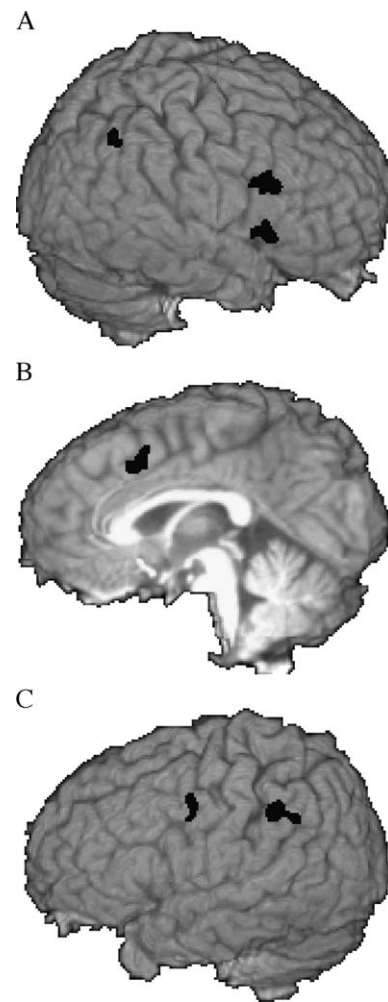


Fig. 5. Common regions of activation for successful response inhibition (Stops) and WM rehearsal: (A) right parietal, dorsolateral prefrontal, and insula; (B) dorsal ACC; (C) left parietal and middle frontal.

Table 4
Common regions of activation for successful response inhibition (Stops) and WM rehearsal

Structure	BA	HS	Volume (μl)	Center of mass		
				x	y	z
Frontal lobe						
Middle frontal	9/46	R	237	38	31	26
Middle frontal	6	L	188	-40	0	43
Anterior cingulate	32	L	261	-3	18	42
Parietal lobe						
Supramarginal	40	L	418	-40	-42	36
Subcortical						
Lentiform or putamen		L	278	-21	8	2
Insula	13	R	239	35	17	1

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

specific to inhibitory control, as the area of common activity in the right DLPFC was neither responsive to WM demands nor predictive of performance. Moreover, the majority of brain regions that were involved in inhibition and were sensitive to the load manipulation were not in the ‘common resources’ inhibition and rehearsal map but instead were specific to the inhibition function. This finding suggests that at least in the current task design, the brain responded to competing demands for the same brain regions by making greater use of task specific or ‘noncommon’ cortical regions. Sylvester et al. (2003) have previously shown that inhibitory control activates both unique and shared (with other cognitive processes such as task switching) cortical regions, with the current study suggesting that the unique regions identified by Sylvester in premotor and prefrontal areas were those called upon during competing demands for common regions.

It remains to be seen whether this result can be generalized to other paradigms, for example, recent literature examining inhibition has suggested that the cognitive processes required for Go/No-go and Stroop-type tasks can be distinguished from those for reducing proactive interference (Friedman and Miyake, 2004). There also remains the possibility that these different forms of inhibition have cortical substrates that interact differently with demands such as increasing WM load (Kok, 1999; West et al., 2002). The similarity of common inhibitory or WM regions in the Bunge et al. (2001), where proactive interference rather than motor inhibition was emphasized, and the current study does provide some encouragement to the generalizability of this phenomenon.

PFC and control

Increasing WM demands made inhibition more difficult, though success was maintained by increasing activation in a number of clusters (both common and unique), located primarily in the DLPFC and dorsal ACC/pre-SMA.

Many models of prefrontal function propose that the role of the PFC in the type of cognitive control tested here is to competitively bias information processing in more posterior or subcortical regions (Duncan and Owen, 2000; Kimberg and Farah, 1993; Miller and Cohen, 2001). For example, the model proposed by Miller and Cohen (2001) argues that “one of the most fundamental aspects of cognitive control and goal directed behavior: [is] the ability to select a weaker, task-relevant response (or source of information) in the face of competition from an otherwise stronger but task-irrelevant one” (p. 170). While this model and others like it have typically used evidence from tasks such as the Stroop, which places greater emphasis on the selective attention element of behavioral inhibition, rather than the suppression of a prepotent motor response (which was relevant in the present task), this process may help explain the present results. For example, as the number of items requiring a ‘withhold’ response increases in the present task, it seems likely that more top-down control is required to maintain these responses in the face of a stronger but ultimately task-irrelevant response (the prepotent response).

This additional activation might be required for response selection of the type described by Rowe et al. (Rowe and Passingham, 2001; Rowe et al., 2000), who argue that selecting a particular item within memory is what activates the DLPFC (Schumacher and D’Esposito, 2002). In the current task, the number of competing responses did not increase; however, the number of items within memory from which to select from did increase. This type of response selection would appear to interact

in some way with the simultaneous requirement to inhibit, as the increases in activation were greater than that for ongoing trial responses. Our own previous studies have indicated that prefrontal activation increases as response selection becomes more difficult, for example, when there is less time to prepare the response (Kelly et al., 2004), or if attention has waned as evidenced by increased response variability (Bellgrove et al., in press).

It appears that our attempt to parametrically manipulate WM demands may have had the effect of parametrically increasing the requirement for top-down control, resulting in significantly increased activation of the DLPFC and interestingly the dorsal ACC/pre-SMA region. Many previous studies have implicated these regions (particularly the DLPFC) in top-down control of processing, including the domains of selective attention (Mathalon et al., 2004; Milham et al., 2003), task-switching (Aron et al., 2004; Sussman et al., 2003), spatial attention (Giesbrecht et al., 2003; Hopfinger et al., 2000), sustained attention (Lawrence et al., 2003; Ortuno et al., 2002), emotional (Boshuisen et al., 2002; Milham et al., 2003), and autonomic control (Critchley et al., 2002, 2003). The finding that activation in this region (along with the right DLPFC) was significantly greater for No-go trials when compared to the Go trials is also consistent with the studies suggesting it monitors for response conflict (Braver et al., 2001; Carter et al., 2001), whereby conflict signals the need for the allocation of additional control by the DLPFC (MacDonald et al., 2000). Carter et al. (2001) indicate that conflict arises from response competition, although this conceptualization makes it difficult to interpret the WM demand sensitivity of this region in the present study, as the likelihood of making the Go or No-go response remained constant. Also, midline activation was responsive to load increases during both WM rehearsal and encoding, suggesting that this region gauges more than response conflict, but may be reflective of the need to increase willed control over behavior (Paus, 2001), or monitoring of autonomic responses that signal the requirement for adaptive control of behavior (Luu and Posner, 2003).

Cortical dissociations

The manipulation of WM demands during inhibition also revealed interesting dissociations with regard to activation in the dorsolateral, parietal, and cerebellar regions. Inhibition-related activation in DLPFC regions increased as a function of WM load, while levels in the cerebellum significantly decreased and parietal regions remained consistent (see Fig. 3). While we have supported the view that the DLPFC plays a modulatory role, incrementing top-down control as required, the role of the more posterior parietal lobe can also be accommodated within this model. Bilateral parietal regions demonstrated sensitivity to increasing WM demands during both the encoding and rehearsal parts of the task, though not during the successful inhibitions. This type of dissociation would support a storage-based role for the parietal region, storing the stimulus–response representations necessary for inhibition, but not part of the executive control itself. Interpretation of the declining cerebellar activity is less straightforward due to the widely debated role of the cerebellum in executive function and cognition generally (Allen and Courchesne, 2003). One perspective developed recently is that the cerebellum acts as a mechanism in the prediction and preparation of mental and motor operations (Courchesne and Allen, 1997). Courchesne and Allen (1997) argue that the cerebellum responds to predictable circumstances, preparing neural networks likely to be required for an upcoming event by

learning predictive stimuli sequences. This type of relationship would not appear likely in the present study as predictive information was not available from our task. Alternatively, activation in the cerebellum might be optimized under conditions of high stimulus or response predictability. For example, the stimulus–response relationship at WM load size 1 in the present study was fairly straightforward, with all stimuli except one item requiring a button press, perhaps encouraging a preparation of this particular stimulus–response pairing. As WM demands were increased, predictability would have decreased and use of a cerebellar mediated preparation function may have diminished in favor of the more top-down type control modulated by the DLPFC.

Implications and conclusions

The results of the present study indicate that the ability to successfully inhibit an increasing number of items held in WM depends on an increase in top-down control of attention. This result gives support to the recent findings of *Perlstein et al.* (2001, 2003) who identified with separate tasks of WM and inhibitory control that participants with schizophrenia had particular difficulty under conditions of either high WM or prepotency demands. As the experimental demands increased and patient's performance began to suffer, a smaller increase in activation of the right DLPFC region was identified using fMRI, suggesting an insufficient ability to increase top-down control. A difficulty exerting high levels of top-down control might also account for clinical symptoms such as ruminative thoughts. For example, studies with cocaine users suggest that cue-induced ruminative thoughts activate a 'WM-like' network of regions (*Bonson et al., 2002; Garavan et al., 2000*), and impaired performance on a central executive or WM task has been associated with rumination induction in a sample of patients suffering from major depression (*Watkins and Brown, 2002*). If ruminative thoughts represent the temporary processing of items in WM, the current research suggests that as these WM demands increase it will take a high level of top-down control to inhibit the attention directed towards them, a capacity showing impairment in both of these groups (*Bolla et al., 2000; Tekin and Cummings, 2002*).

In conclusion, the present study offers a new insight into how the network of regions activated for inhibitory control copes with increasing WM loads. As WM demands were parametrically increased, significant increases were seen in a number of cortical areas, most importantly for behavioral control, in both midline (dorsal ACC/pre-SMA) and dorsolateral prefrontal regions. This finding provides support for the suggestion that top-down attentional control involves a modulatory role for the DLPFC, where weaker stimulus–response relationships must be supported in the face of competition from stronger, prepotent ones and potentially that the requirement for this type of top-down support is signaled by the dorsal ACC or pre-SMA's monitoring of the requirement for adaptive control. Our findings suggest that while there were some common regions of activation for WM and inhibition, utilizing unique task-specific cortical areas appeared especially important for successful behavioral performance. From these results, we conclude that tasks can interfere and can require similar areas of cortex (as revealed within the limits of fMRI methods and resolution) but that the brain appears to adapt to these competing demands by using task-related areas which are not shared. The ability to modulate activation in both unique and shared cortical regions appears critical to maintaining the level of top-down

control, an important finding for our understanding of the cognitive deficits common in a range of clinical disorders but also symptoms such as ruminative thoughts, where the control over items currently being held in WM appears critical.

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