A Parametric Manipulation of Central Executive Functioning

H. Garavan[1], T.J. Ross[1], S.-J. Li[2] and E.A. Stein[1,2]

[1]Department of Psychiatry and [2]Biophysics Research Institute, Medical College of Wisconsin, Milwaukee, WI, USA

The central executive is both an important and poorly understood construct that is invoked in current theoretical models of human cognition and in various dysexecutive clinical syndromes. We report a task designed to isolate one elementary executive function, namely the allocation of attentional resources within working memory. The frequency with which attention was switched between items in working memory was varied across different trials, while storage and rehearsal demands were held constant. Functional magnetic resonance imaging revealed widespread areas, both prefrontal and more posterior, that differentially activated as a function of a trial's executive demands. Furthermore, areas that differed as a function of executive demands tended to lie adjacent to areas that were activated during the task but that did not so differ. Together, these data suggest that a distributed neuroanatomy, rather than a specific and unique locus, underlies this attention switching executive function.

Introduction

The last two decades have witnessed a dramatic increase in research on working memory (WM). Theoretical advances have evolved from the concept of a short-term memory, in which items are stored for a short period of time for later recall, to a conceptualization of active, on-line processing or manipulation of those stored items. New tasks that stress the interplay between dynamic processing and storage now stand among the best predictors of intelligence, reasoning and comprehension abilities. Correlations between standard IQ measures and WM abilities of 0.8 or greater are not uncommon (Carpenter *et al.*, 1989; Kyllonen *et al.*, 1990; Suss *et al.*, 1996). As a consequence, the WM concept is now well established as being of central importance in cognitive psychology and is, for example, an essential component of production system models (Anderson, 1983).

An understanding of WM processes, with particular emphasis on executive functioning, also has important clinical significance. Various tests including dual-task performance, Stroop tasks, the Wisconsin Card Sorting Task (WCST), delayed alternation, assorted WM tasks, and tests of inhibitory control have implicated executive dysfunction in patients with dementia of the Alzheimer's type, Parkinson's disease, schizophrenia, early treated PKU, autism, ADHD, and fragile-X syndrome in women (Baddeley *et al.*, 1991, 1996; Dalrymple-Alford *et al.*, 1994; Diamond, 1996; Dunbar *et al.*, 1995; Pennington *et al.*, 1996; Weinberger *et al.*, 1996).

The role of WM and executive functioning constructs in clinical and individual differences research may, in part, have prompted interest in identifying the neuroanatomical locations and mechanisms that subserve both. Most *in vivo* neuroimaging research has adhered to the current prevailing model that proposes two short-term storage slave-systems, the phonological loop and visuospatial sketchpad, and a 'coordinator', labeled the central executive (Baddeley *et al.*, 1974; Baddeley, 1986). Baddeley has likened the central executive to Norman and Shallice's 'supervisory attentional system', thus emphasizing the role that the central executive plays in allocating attentional resources (Norman *et al.*, 1986; Baddeley, 1993). It is important to note that the central executive has proven much less tractable to investigation than have the WM slave-systems, prompting Baddeley to refer to it as the area of residual ignorance within his tripartite model. Presumably, this is due, in no small part, to the difficulty engendered in attempting to divorce executive functions from other WM functions; the system, by design, being meant to work as an integrated whole.

The Central Executive

As listed above, numerous tasks have been proposed as tests of executive functioning. Within the clinical domain, executive functions are commonly equated with strategic planning or problem solving. These are, however, blanket terms that presumably are subserved by many more elementary cognitive operations. Another approach to defining and testing executive functions, and one adopted in the present study, is inspired theoretically by current models of WM (Pennington *et al.*, 1996). Consequently, our working definition of the central executive is concordant with the coordinator or attentional allocator of Baddeley's model.

In attempting to identify their anatomical locus or loci, cognitive neuroimaging experiments that have explicitly operationalized executive functions have done so in various ways, including dual-task coordination (D'Esposito *et al.*, 1995), task switching (Evans *et al.*, 1996; Lauber *et al.*, 1997), memory updating (Salmon *et al.*, 1996), on-line manipulation of items (Collette *et al.*, 1999), and response sequencing, monitoring and manipulation (Owen *et al.*, 1996). Examples of functional neuroimaging studies in which attention allocation has been the explicit focus include tests of dual-task performance, wherein subjects must perform two tasks concurrently (D'Esposito *et al.*, 1995; Goldberg *et al.*, 1996), and alternating task switching, in which subjects must alternate between two tasks (Evans *et al.*, 1996; Klingberg *et al.*, 1997).

A consensus implicating dorsolateral prefrontal cortex as critical for executive functioning has emerged as this region has been observed in a number of studies using a number of different tasks (D'Esposito *et al.*, 1995; Owen *et al.*, 1996; Salmon *et al.*, 1996; Collette *et al.*, 1999). However, it would be a mistake to presume that executive functions are located solely in prefrontal regions. Those studies that have localized executive functions to the dorsolateral prefrontal cortex have also observed extensive parietal, premotor, cingulate, occipital and cerebellar activation. Consistent with these findings, recent functional imaging studies of 'classic' executive tasks such as the Tower of London, the WCST, and Raven's Progressive Matrices

© Oxford University Press 2000

Test reveal extensive activation in frontal, as well as temporal, parietal and occipital lobes and in the cerebellum (Berman *et al.*, 1995; Baker *et al.*, 1996; Nagahama *et al.*, 1996; Prabhakaran *et al.*, 1997).

The Present Study

In the present paper, we attempt to isolate central executive functioning by holding constant on-line storage demands while varying the on-line manipulation of items in WM. The task probed executive functions by isolating volitional switches of attention between items (specifically, running counts) residing in WM. Our previous research with a variant of this task has demonstrated a sizeable time cost when switching from one count to another (Garavan, 1998). The switching cost was calculated by comparing the time to update two different counts in succession relative to updating the same count twice in succession. The existence of this time cost, which persists after intensive task practice, suggests that people do not have immediate and simultaneous access to all items currently in working memory. Instead, there is an 'internal' focus of attention that is large enough for just one WM item (i.e. count) at a time, consistent with Cowan's model of an attentional spotlight within WM (Cowan, 1988, 1993). Thus, the task required that attentional resources be reallocated from one count to another when a switch between counts was made.

One important feature of the task is that the attention switching parameter can be manipulated while holding constant the number of items in WM (all trials require two counts to be stored) and the amount of subvocal rehearsal employed throughout the trial (described in greater detail below). A second advantage is that the executive function is well characterized. In contrast, a comparison of, say, dual-task performance with single-task performance as a means to investigate executive functions, isolates more than attention switching. The dual-task requires one to process two sets of inputs, to perform the necessary mental processing of each task, and to provide two sets of responses. Both the added demands and coordination at each of these stages, plus on-line strategic allocation of limited resources, exist only in the dual-task condition. Similarly, the alternating task switching paradigm, when compared to single-task performance, often requires memory of the alternation order. The counting task in the present study has no such additional memory requirement, as the stimuli unambiguously cue which count is to be updated (described below).

Theoretically, we conceive of a volitional switch of attention within WM as an elementary executive function or control process. By focusing on one well-characterized executive function, we remain agnostic as to whether the central executive should be characterized as an independent psychological entity or whether the central executive is no more than a collective term for cognitive control processes (Baddeley, 1998; Parkin, 1998). We wished to test if this particular executive function was localized to a specific brain region or if it was associated with activation in broadly distributed regions that have previously been demonstrated to subserve WM task performance. It should be noted that the present study only addresses attention switching within verbal WM; it will be important to demonstrate that the results reported herein are also observed for attention switching within other WM domains.

To isolate functional activation associated with this executive function, a parametric manipulation of executive demands was employed. Parametric manipulations offer many advantages over the more common and sometimes questionable subtraction strategy (Sternberg, 1969; Jennings *et al.*, 1997; Price *et al.*, 1997). Through the logic of additive factors, one does not attempt to include or exclude the process of interest but rather to modulate the degree to which the process is present. The modulation of a functional signal associated with an executive process also allows one to characterize the functional relationship between the process of interest and regional brain activation. Localization of function using parametric manipulations has been previously demonstrated in sensory (Binder *et al.*, 1994), motor (Rao *et al.*, 1996) and cognitive domains (Jonides *et al.*, 1997; Carlson *et al.*, 1998).

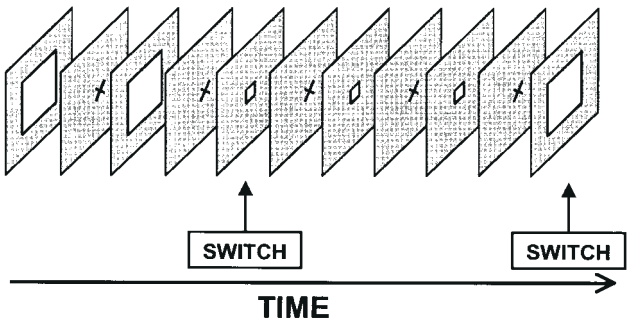

Figure 1. Schematic of the task. Subjects maintained two running counts of large and small squares during a trial. The order in which the squares were presented dictated whether or not a switch of attention between the two counts being stored in WM was required.

Table 1
The number of switches between counts for the different levels of switching frequency (the number of switches per trial was rounded down when the division left a remainder)

Switching frequency	Number of switches	Example: trial with 16 squares
High	total number of squares/2	no. of switches = 8
Medium	total number of squares/4	no. of switches = 4
Low	1 switch	no. of switches = 1

Materials and Methods

Eleven right-handed subjects participated in this study (four female; mean ± SD age: 28.5 ± 8.2, range: 19–41). All gave informed consent, which was approved by the institutional review board of the Medical College of Wisconsin. Subjects were instructed that on each trial they would be presented with a sequence of large and small squares, presented in random order. Their task was to keep a count of how many large squares and how many small squares were presented and to report these counts at the end of each trial, which contained from 11 to 16 squares. Each square was presented for 1500 ms and successive squares were separated by a 100 ms fixation point (an 'X' in the center of the screen). The purpose of the fixation point was to clearly delineate successive presentations of the squares. At the end of each trial, using a joystick to move a cursor along a number line, subjects indicated how many large and small squares were presented. Feedback, in the form of the correct counts, was then presented. Subjects were given 12 s in which to make their responses and feedback was presented for just 1 s. A 15 s rest period followed the feedback. At the end of the rest period a change in the fixation point signaled the start of the next trial.

Three trials for each of six trial lengths (11–16 squares) were randomly ordered. The order in which the squares were presented within a trial determined how many switches of attention between the counts were required (see Fig. 1 for task schematic). The 18 trials were comprised of six 'High', six 'Medium' and six 'Low' switching frequency trials (see Table 1). All subjects were instructed to rehearse the current values of both counts following each count update (i.e. after each individual square was presented). Rehearsing both counts in this manner

ensured equal amounts of subvocal rehearsal during all trials and is adopted spontaneously by almost all subjects (Garavan, 1998). The sequence of 18 trials was presented in two runs of nine trials. A 2 min rest period separated these runs. Rest periods of 36 s were included at the start and end of each run. In total, the experiment lasted ~25 min.

fMRI Parameters

Contiguous 7 mm sagittal slices covering the entire brain were collected using a blipped gradient-echo, echo-planar pulse sequence (T_E = 40 ms; T_R = 4800 ms; FOV = 24 cm; 64 × 64 matrix; 3.75 mm × 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 radio-frequency head-coil (Wong *et al.*, 1992). Foam padding was used to limit head movements within the coil. High-resolution spoiled GRASS anatomic images were acquired prior to functional imaging to allow subsequent anatomical localization of functional activation. 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 radio-frequency head-coil.

fMRI Analyses

All data processing was conducted with the software package AFNI v. 2.2 (Cox, 1996). In-plane motion correction and edge detection algorithms were first applied to the functional data. The percentage change in signal produced during the trials was calculated relative to the average signal during the rest periods at the start and end of each run. The average signal produced during the performance of each trial was based on only those images acquired during the counting portion of each trial (images acquired while the subject reported the final count values or during the rest periods between trials were excluded from the functional analyses). The average percentage change in signal for all trials of each switching density was calculated. These change scores, three per voxel per subject, served as the basic unit of analysis and are referred to subsequently as 'activation'.

Activation maps were converted to a standard stereotaxic coordinate system (Talairach and Tourneaux, 1988), and spatially blurred using a 4.2 mm full-width-at-half-maximum isotropic Gaussian filter. Among those regions activated by the task, we were interested in identifying both those that differed as a function of switching frequency and those that did not. Consequently, basic task activation maps for each level of switching frequency were identified with one-sample *t*-tests against the null hypotheses of no change in activation. These *t*-test maps were thresholded with alpha set to 0.05 and combined such that a voxel was included in the task map if significant in any one *t*-test map. To identify regions that differed in activation across switching frequency, a two-way, repeated-measures, voxelwise ANOVA was performed within this task map with switching frequency treated as a fixed factor and subject as a random factor. A voxel was deemed significant if its associated *P*-value was 0.01 or less and if it was one of a larger cluster of significant, contiguous voxels of minimum size 200 µl (approximately twice the size of the originally acquired voxels). The advantages of combining a voxel-based threshold with a minimum cluster size have been described elsewhere (Forman *et al.*, 1995). These criteria, while incorporating the spatial blurring of the Gaussian filter, yielded a voxelwise false positive level of 0.0005. Simulations revealed that fewer than one cluster conforming to our statistical and cluster size criteria would have been observed by chance (on average, 0.74 clusters were observed per simulation). Once identified, the mean voxel activation within each cluster was calculated for each level of switching frequency. ANOVAs with pairwise contrasts were then performed for each cluster on the mean activation values.

Two criteria were employed to identify activated voxels that appeared not to differ with switching frequency. First, a voxel had to be significant in all three one-sample *t*-tests (one per switching frequency) described above. Second, activation in each of the three switching conditions had to fall within 28.6% of their average. This percentage is based on the average differences in activation calculated for those voxels that were significantly different based on the above ANOVA. The activation scores for these significantly different voxels varied, on average, by 95.4%. Voxels that could reasonably be assumed to be similar in activation were required to differ by no more than 30% of this amount, hence 28.6%.

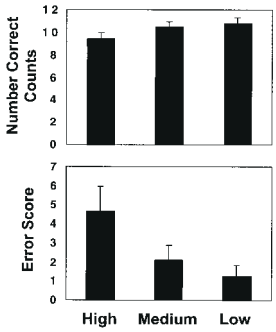

Figure 2. Mean (± SEM) accuracy, measured as the number of correct trials (top) or the errors in reported counts (bottom), for each level of switching frequency. Both graphs illustrate that performance declined as the number of switches increased.

Performance Analyses

Two measures of accuracy were employed. In the first, accuracy was determined by the number of correct counts, allowing subjects to score a maximum of two points per trial. An alternative to this first measure, that scored each trial as correct only if subjects reported both counts correctly, yielded identical results and will not be reported. The second measure incorporated how inaccurate subjects were in their reported counts. The absolute differences between the reported counts and the true counts were summed, providing an error measure for each trial. For both measures, accuracy scores were summed for all six trials at each level of switching frequency.

Results

Task Performance

One-way, repeated-measures ANOVA revealed a significant main effect for switching frequency on both the number of correct counts [$F(2,20) = 6.2$, $P = 0.008$)] and the count error measure [$F(2,20) = 8.3$, $P = 0.002$] (see Fig. 2). Differences in accuracy were in the expected direction (High < Medium < Low for the number of correct counts and High > Medium > Low for the error measure) but only with the latter measure were any of the *post hoc* Scheffé tests significant (High versus Low: $P = 0.05$).

All trials were included in the functional analyses, since previous data showed trials in which errors in counting were made to be comparable to error-free trials (Garavan, 1998). For example, in a self-paced format, the response time cost incurred when switching between counts was the same in both incorrect and correct trials, the supposition being that though a tabulation error was made, subjects nonetheless maintained two running counts throughout the trial. In the present data, this was borne out by the nature of the errors in the incorrect trials. Totaling across subjects, of the 42 incorrect trials, on just 10 (24%) were both counts incorrect. Furthermore, for 71% of all the incorrect counts, the reported values were within ±1 of the correct values.

Functional Activation

Table 2 lists those regions that differed in activation as a function of switching frequency. In all cases, activation increased with switching frequency, i.e. High > Medium > Low. Discrete areas of activation, localized to the right middle frontal gyrus and more posterior bilateral inferior frontal gyrus, were observed in the prefrontal cortices. However, those regions, presumed to underlie the central executive processes required by the task, were not restricted to prefrontal cortex. Noticeably large areas of activation in left parietal (especially, inferior parietal lobule and precuneus) and left cerebellar regions were observed, as was activation in occipital, temporal and subcortical (thalamus and

Table 2
Clusters identified to vary as a function of switching frequency

Structure	Side	Center-of-mass (*x,y,z*)	Brodmann area	Cluster vol. (μl)	Mean change in activation				H vs. M	H vs. L	M vs. L
					H	M	L	*P*	P	*P*	*P*
Frontal lobe											
Inf. fr. g.	L	–43,6,25	9/6	1196	0.312	0.089	0	**	(0.08)	0.01	(0.36)
	R	45,5,31	9/6	800	0.548	0.356	0.152	**	(0.38)	0.02	(0.33)
Ant. cingulate/sup. fr. g.	B	3,9,49	6/32/24	777	0.519	0.255	0.175	**	(0.20)	(0.07)	(0.86)
Mid. fr. g.	R	31,42,22	10	481	0.445	0.168	–0.002	*	(0.35)	(0.08)	(0.67)
Precentral g.	L	–26,–8,48	6	445	0.248	0.098	0.005	***	(0.23)	0.03	(0.56)
Temporal lobe											
Mid. temp. g.	R	46,–29,–1	22	425	0.248	0.062	0.005	**	(0.17)	0.04	(0.78)
Hippocampus/parahippo. g	L	–28,–34,–5		344	0.102	–0.119	–0.124	**	0.005	0.004	(0.94)
Parietal lobe											
Inf. par. lobule/supramarginal G.	L	–37,–37,34	40	1400	0.292	0.131	0.050	****	0.018	0.0004	(0.33)
	L	–37,–50,50	40	643	0.317	0.146	0.026	****	0.05	0.0006	(0.21)
	R	37,–35,38	40	247	0.308	0.196	0.074	**	(0.40)	0.03	(0.35)
Precuneus	L	–21,–65,40	7	1239	0.345	0.159	0.085	****	(0.12)	0.02	(0.70)
Postcentral g.	L	–13,–42,67	7	509	0.114	–0.297	–0.443	**	0.04	0.004	(0.64)
Sup. par. lobule	L	–32,–62,50	7	246	0.319	0.086	0.025	**	(0.11)	0.03	(0.85)
Occipital lobe											
Cuneus	L	–6,–84,18	18	586	0.416	0.165	0.067	**	(0.30)	(0.10)	(0.83)
	R	3,–66,8	30	422	0.637	0.019	–0.107	**	(0.10)	0.04	(0.90)
	L	–28,–80,26	19	307	0.270	0.053	–0.019	**	(0.20)	(0.07)	(0.83)
Sub-cortical											
Thalamus/dorsomedial N.	B	–1,–19,12		535	0.555	0.174	0.160	**	(0.07)	(0.06)	(0.99)
Caudate	R	19,–8,22		247	0.267	0.205	0.049	*	(0.71)	0.02	(0.13)
Cerebellum											
Post. lobe/fusiform g.	L	–35,–58,–17	37	2273	0.403	0.008	–0.143	****	0.0006	<0.0001	(0.25)
Ant. lobe	L	–29,–35,–27		308	0.267	–0.016	–0.257	*	(0.14)	0.003	(0.24)

Abbreviations: Ant., anterior; fr., frontal; g., gyrus; inf., inferior; mid., middle; n., nucleus; occ., occipital; par., parietal; post., posterior; sup., superior; temp., temporal.

*$P < 0.001$; **$P < 0.0001$; ***$P < 0.00001$; ****$P < 0.000001$. Center-of-mass coordinates specify locations in millimeters relative to the anterior commissure. Positive values are to the right of, anterior to, and superior to the anterior commissure. ANOVA results, means, and pairwise contrasts (Scheffé test) for the three switching conditions are shown (H = High, M = Medium, L = Low). For non-significant contrasts, *P*-values are provided within parentheses.

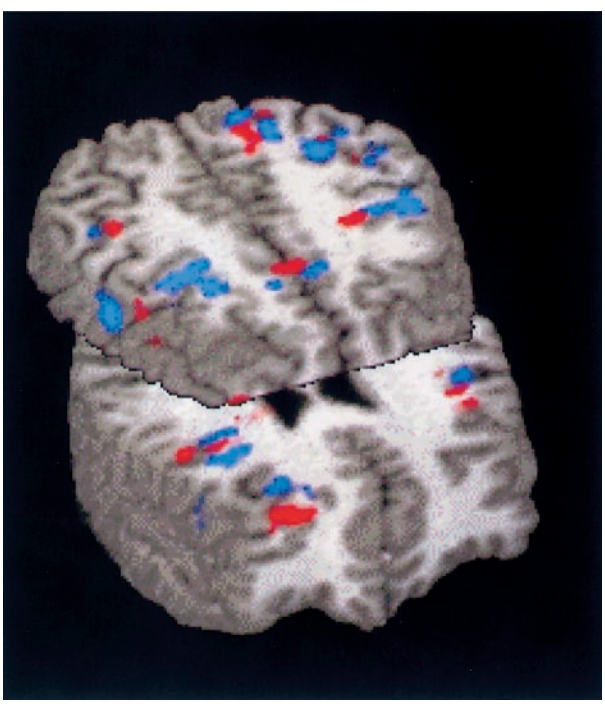

Figure 3. Areas of significant activation during performance of the task are shown on one subject's anatomy. The top axial slice is 42 mm superior to the anterior commissure (AC), the lower axial slice is 25 mm superior to the AC, and the coronal slice is 42 mm anterior to the AC. Areas in red differed as a function of the attention switching parameter, while blue areas were consistently activated by the task but did not vary with switching frequency. Note that the red and blue areas tended to be co-localized in regions previously thought to underlie WM performance, including the inferior parietal lobule, premotor, SMA, and inferior and middle frontral gyri.

caudate) areas (see Fig. 3). Prefrontal and parietal regions were also strongly represented among those activated in performance of the task but not differing as a function of switching frequency (see Table 3 and Fig. 3). In contrast, no such regions of activation were observed in the cerebellum or occipital lobe.

Discussion

Performance of a new WM task, one that has not previously been used in a functional neuroimaging study, produced a distributed network of cerebral activation. Regional activation was largely consistent with the circuitry thought to underlie WM function, incorporating dorsolateral prefrontal, premotor and parietal areas [reviewed elsewhere (D'Esposito *et al.*, 1998; Jonides *et al.*, 1993)]. As an internal control, a number of activation clusters, although significantly activated by the task at each level of switching frequency, did not increase in activation with

Table 3
Clusters activated by the task but that did not vary as a function of switching frequency. Means for the three switching conditions are shown (H = High, M = Medium, L = Low)

Structure	Side	Center-of-mass (*x,y,z*)	Brodmann area	Cluster vol. (μl)	Mean change in activation		
					H	M	L
Frontal lobe							
Fr. limbic area/medial fr. g.	B	–1,5,49	24/6	2052	0.481	0.413	0.360
Inf. fr. g./precentral g.	L	–44,–7,38	9/6	1206	0.315	0.300	0.286
Mid. fr. g./precentral g.	R	31,–1,44	6	1824	0.326	0.304	0.256
Mid. fr. g.	R	25,28,24	9	839	0.271	0.281	0.265
Inf. fr. g.	R	37,10,26	9	348	0.367	0.352	0.275
	R	51,19,16	45	229	0.482	0.431	0.427
Precentral g.	R	45,4,14	44	837	0.303	0.321	0.286
	R	54,–3,37	6	338	0.619	0.574	0.446
	R	37,–1,26	6	219	0.237	0.234	0.186
Temporal lobe							
Mid. temp. g.	R	43,–51,4	19	317	0.229	0.221	0.246
	R	50,–62,8	39	207	0.483	0.375	0.429
Parietal lobe							
Inf. par. lobule	R	43,–36,45	40	601	0.269	0.254	0.210
	L	–35,–49,41	40	537	0.250	0.233	0.199
	L	–49,–40,42	40	261	0.247	0.228	0.205
Sup. par. lobule	L	–25,–63,43	7	406	0.312	0.263	0.249
Precuneus	L	–20,–73,40	7	352	0.348	0.278	0.341
	R	22,–59,47	7	313	0.285	0.263	0.289
Limbic/thalamic							
Cingulate g.	B	4,–9,28	24	212	0.216	0.220	0.205
Thalamus/dorsolateral n.	R	8,–16,16		412	0.338	0.295	0.268
Pulvinar	R	21,–25,0		211	0.187	0.237	0.238

Switching frequency was not significant ($P > 0.05$) for any cluster. Abbreviations as in Table 2.

switching frequency. Such clusters argue against a generalized, indiscriminate increase in activation associated with increased effort. By manipulating the extent to which attentional resources within WM were dynamically allocated in different trials, we sought to isolate the central executive component of WM. Activation associated with the executive process of attentional allocation was broadly distributed, including both frontal and posterior regions.

The Role of the Frontal Lobes in Executive Functioning

The special status of the frontal lobes in executive processes in humans rests upon both studies of patients with frontal insult and newer imaging techniques of intact subjects performing 'executive' tasks. The present study has identified frontal lobe regions in Brodmann areas 9, 10 and 6 specific to the executive demands of the task. Particular importance of the right middle frontal gyrus activation is suggested by similarly located activation in a recent study that attempted to isolate executive functions by contrasting a task that required the short-term storage of items with one that required both the short-term storage and manipulation of items (Collette *et al.*, 1999). The other frontal activations included premotor, pre-SMA and bilateral inferior frontal gyrus. Premotor and pre-SMA activations have previously been reported for WM tasks (D'Esposito *et al.*, 1998) and bilateral inferior frontal gyrus activation has been reported in performance on a version of the WCST optimized to better identify activation during set shifting (Konishi *et al.*, 1998).

Disentangling specific central executive activations from other WM activations may best be accomplished with comparisons across tasks that differentially engage both the central executive and other WM functions. Convergence might be especially critical for the central executive, given that it remains a vague construct (Morris, 1996). We have made steps in this direction by contrasting the present test of attentional control with a test of inhibitory control (Garavan *et al.*, 1999); further convergence was observed with the work of Collette and colleagues (Collette *et al.*, 1999). In all three tasks, activation occurred in the right middle frontal gyrus and in the left inferior parietal lobule. This convergence is notable given the differences in tasks, imaging modality, experimental design and analyses. While there is a risk of reifying these overlapping areas, one hypothesis is that they may constitute necessary regions for executive functioning. Further insights into identification of those regions that are not just activated by executive functions but are necessary for their performance may be obtained through study of various lesion populations.

Distributed Circuitry Underlying Central Executive Functions

One of the more striking findings of the present study is that activation, putatively underlying central executive functioning, was widely distributed and, in some cases, adjacent to those regions that were activated but that did not differ with switching frequency. Included in this distributed circuitry were extensive parietal areas, mostly in the left hemisphere, cerebellar and subcortical structures, including the caudate and the dorsomedial nucleus of the thalamus, a nucleus that projects principally to prefrontal cortex. Activation was also observed in the cuneus and in the temporal lobe (see Table 2).

One potential interpretation for this distributed activation is that we have failed to isolate the attention switching executive function but instead have mapped a full WM system, one that contains both executive functions and other WM processes such

as short-term storage and rehearsal. This presumes that the manipulation of attention switching modulated the entire WM circuit, which would seem to be at odds with the existence of regions that were consistently activated by the task but that did not so differ. Certain features of the task also argue against this alternative explanation. First, all trials required two counts to be stored and the manner in which subjects rehearsed the counts (rehearsing both count values after each count update) should have guaranteed equal subvocal rehearsal in all trials, irrespective of switching frequency. Furthermore, the amount of switching required in a trial was unpredictable, thus the attention and vigilance maintained by subjects should have held constant across trials of different switching frequencies. However, it is possible that as the trial progressed, subjects may have learned that the density of switches up to an intermediate point in the trial predicted how many more switches would be required. With this realization, certain task-related processes may have diminished.

An alternative explanation is that executive functions may be truly distributed and may be served by the same regions that participate in other cognitive functions. For example, a recent study showed that the areas involved in task-set shifting may be those very same regions that perform the tasks between which one is shifting (Kimberg *et al.*, 1999). However, it is to be expected that this observation may be dependent upon the tasks that one employs, as dual-task performance may engage prefrontal regions not activated during the performance of either task alone (D'Esposito *et al.*, 1995). This latter finding may also be affected by one's choice of task as single WM tasks have frequently been observed to activate prefrontal regions (see Klingberg, 1998). An additional consideration is that the similarity between the observed activation pattern and previously established WM activation maps may be attributable to a central executive contribution to those WM maps; WM maps are based upon tasks that invariably engaged executive functions in their performance. Thus, previously observed WM maps may, implicitly, in part or in whole, also be maps of the central executive. Such a conclusion would argue against a neuroanatomical locus unique to the executive function, suggesting instead that executive functions are accomplished throughout the structures that underlie WM performance.

Distributed activation is not uncommon among those tasks attempting to isolate executive functioning. For example, the dual-task study of D'Esposito and colleagues observed activation in an anterior cingulate and left premotor region as well as in bilateral dorsolateral prefrontal cortex (D'Esposito *et al.*, 1995). Furthermore, the nature of the task subtractions did not allow the possibility of parietal activations associated with dual-task performance to be discounted. The memory updating condition of Salmon and colleagues, when compared to a phonological short-term storage task, revealed bilateral activations in the middle frontal gyrus (R > L) and in right frontopolar cortex (Salmon *et al.*, 1996). However, extensive non-frontal activations were also reported in the right inferior parietal and angular gyri, left supramarginal gyrus, right thalamus, cuneus/precuneus and cerebellum. Collette and colleagues also found parietal activation associated with executive functions (Collette *et al.*, 1999). In fact, their focus of parietal activation overlapped with the parietal activation of the present study and fell just 7 mm away from our center-of-mass. The existence of this parietal activation is at odds with an hypothesis that ascribes only a storage role to this region in the performance of a verbal WM task (Awh *et al.*, 1996; Smith *et al.*, 1997). On the presumption that storage and rehearsal demands were equal in all trials, the increase in parietal activation corresponding to the attention switching parameter suggests a parietal lobe involvement in executive functions. Jonides and colleagues have suggested that the posterior parietal activation that they have observed in verbal WM tasks may reflect short-term storage processes or may 'indicate an involvement of parietal mechanisms in shifting attention from internal representations of one item to another as they are rehearsed' (Jonides *et al.*, 1998). The present study, which observed some parietal clusters that did not vary as a function of switching frequency and other parietal clusters that did vary as attention switching was manipulated independent of storage demands, finds support for both roles. Finally, as previously noted, neuroimaging of classic executive tasks and other cognitively inspired executive tasks also show extensive cortical activation that can range from prefrontal to primary visual areas (Berman *et al.*, 1995; Baker *et al.*, 1996; Nagahama *et al.*, 1996; Owen *et al.*, 1996; Prabhakaran *et al.*, 1997).

One conclusion from these data might be that the neuroanatomical substrate of the central executive may prove specific to the executive function that is being experimentally manipulated. If the attention switching function of the present study is identifed with the areas involved in other WM functions (i.e. 'executive' areas tended to fall near to 'task' areas; see Fig. 3) and, for example, the task set shifting function studied by Kimberg and colleagues is identifed with the areas activated in performance of the tasks between which one is shifting (Kimberg *et al.*, 1999), then the central executive may be better described in terms of process than in terms of location. That is, the hallmark of an executive function may be neither a specific gyrus nor circuit, but might instead be a functional change in the neuroanatomy underlying the task to which the executive function is being applied. Clearly, more data, addressing more well-characterized executive functions are needed.

A potential confounding factor for the interpretation of this study is that the manipulation of attention switching will also affect the difficulty of the task. Previous research has suggested, however, that one can dissociate activations specific to the manipulation of a task parameter from activations associated simply with increased difficulty [e.g. manipulating WM demand has a different effect on functional anatomy than degrading the presentation quality of the memoranda (Barch *et al.*, 1997); see also D'Esposito *et al.* (D'Esposito *et al.*, 1995)]. For now, we remain unconvinced that 'difficulty' stands as a true alternative hypothesis for the attention switching manipulation effect and suggest, instead, that it is a descriptor of the manipulation's consequences; trials with lots of attention switching are more difficult but for a known reason, namely the frequency of engagement of an effortful attention switching mechanism.

Conclusion

The challenge remains to identify those elementary functions that constitute the arsenal of the central executive. From the combination of such elementary functions, the apparent complexity of human cognition may emerge (Simon, 1969). Such a gradualistic approach is being pursued with behavioral tasks (Baddeley, 1996). With this taxonomy in hand, one can then proceed to determine if there is a distinct neuroanatomical basis for each and if these bases overlap or are unique for different executive functions. The present findings suggest a broadly distributed functional basis for an attention switching function. An understanding of the commonalties and differences in the

circuitry of different executive functions may inform the common and unique symptoms of various neurological insults.

Notes

The assistance of Ray Hoffmann and J. F. Kussmann is gratefully acknowledged. Supported by NIDA grants DA09465 and DA10214 and CRC RR-00058. Address correspondence to Hugh Garavan, Ph.D., Department of Psychology, Trinity College, Dublin 2, Ireland. Email: hugh.garavan@tcd.ie.

References

Anderson JR (1983) The architecture of cognition. Cambridge, MA: Harvard University Press.

Awh E, Jonides J, Smith EE, Schumacher EH, Koeppe RA, Katz S (1996) Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. Psychol Sci 7:25–31.

Baddeley AD (1986) Working memory. Oxford: Clarendon Press.

Baddeley AD (1993) Working memory or working attention. In: Attention: selection, awareness, and control. A tribute to Donald Broadbent (Baddeley AD, Weiskrantz L, eds), pp. 152–170. Oxford: Oxford University Press.

Baddeley AD (1996) Exploring the central executive. Quart J Exp Psychol 49A:5–28.

Baddeley AD (1998) The central executive: a concept and some misconceptions. J Int Neuropsychol Soc 4:523–526.

Baddeley AD, Hitch, G (1974) Working memory. In: Recent advances in learning and motivation (Bower GA, ed.), pp. 47–90. New York: Academic Press.

Baddeley AD, Della Sala S (1996) Working memory and executive control. Phil Trans R Soc Lond B351:1397–1404.

Baddeley AD, Bressi S, Della Sala S, Logie R, Spinnler H (1991) The decline of working memory in Alzheimer's disease: a longitudinal study. Brain 114:2521–2542.

Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frawckowiak RSJ, Robbins TW (1996) Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 34:515–526.

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD (1997) Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 35:1373–80

Berman KF, Ostrem JL, Randolph C, Gold J, Goldberg TE, Coppola R, Carson RE, Herscovitch P, Weinberger DR (1995) Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. Neuropsychologia 33:1027–1046.

Binder JR, Rao SM, Hammeke TA, Frost JA, Bandettini PA, Hyde JS (1994) Effects of stimulus rate on signal response during functional magnetic resonance imaging of auditory cortex. Cogn Brain Res 2:31–38.

Carpenter PA, Just MA (1989) The role of working memory in language. comprehension. In: Complex information processing: the impact of Herbert A. Simon (Klahr D, Kotovsky K, eds), pp. 31–68. Hillsdale, NJ: Lawrence Erlbaum.

Carlson S, Martinkauppi S, Rama P, Salli E, Korvenoja A, Aronen HJ (1998) Distribution of cortical activation during visuospatial n-back tasks as revealed by functional magnetic resonance imaging. Cereb Cortex 8:743–752.

Collette F, Salmon E, Van der Linden M, Chicherio C, Belleville S, Degueldre C, Delfiore G, Franck G (1999). Regional brain activity during tasks devoted to the central executive of working memory. Cogn Brain Res 7:411–417.

Cowan N (1988) Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. Psychol Bull 104:163–191.

Cowan N (1993) Activation, attention, and short-term memory. Mem Cognit 21:162–167.

Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.

Dalrymple-Alford JC, Kalders AS, Jones RD, Watson R W (1994) A central executive deficit in patients with Parkinson's disease. J Neurol Neurosurg Psychiat 57:360–367.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. (1995) The neural basis of the central executive system of working memory. Nature 378:279–281.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J (1998) Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res 7:1–13.

Diamond A (1996) Evidence for the importance of dopamine for prefrontal cortex functions early in life. Phil Trans R Soc Lond B351: 1483–1494.

Dunbar K, Sussman D (1995) Toward a cognitive account of frontal lobe function: simulating frontal lobe deficits in normal subjects. In: Annals of the New York Academy of Sciences (Grafman J, Holyoak KJ, Boller F, eds), pp. 289–304.

Evans JC, Lauber EJ, Meyer DE, Rubinstein J, Gmeindl L, Junck L, Koeppe RA (1996) Brain areas in the executive control of task switching as revealed by PET. Soc Neurosci Abstr 22:7.

Forman SD, Cohen JD, Fitzgerald M., Eddy WF, Mintun MA, Noll DC (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 33:636–47.

Garavan H (1998) Serial attention within working memory. Mem Cognit 26:263–276.

Garavan H, Ross TJ, Stein EA (1999) An fMRI investigation of central executive functions. Proceedings of the Cognitive Neuroscience Society, April, Washington, DC.

Goldberg TE, Fleming K, Berman KF, Van Horn J, Esposito G, Ostrem J, Gold JM, Weinberger DR (1996) Neurophysiology of dual-task performance: a PET O15 study. Soc Neurosci Abstr 22:967.

Jennings JM., McIntosh AR, Kapur S, Tulving E, Houle S (1997) Cognitive subtractions may not add up: The interaction between semantic processing and response mode. Neuroimage 5:229–239.

Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S, Koeppe RA (1997) Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 9:462–475.

Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, Marshuetz C, Wliis CR (1998) The role of parietal cortex in verbal working memory. J Neurosci 18:5026–5034.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun M (1993) Spatial working memory as revealed by PET. Nature 363:623–625.

Kimberg DY, Aguirre GK, D'Esposito M (1999) Neural activity associated with task-switching: an fMRI study. Proceedings of the Cognitive Neuroscience Society, April, Washington, DC.

Klingberg T (1998) Concurrent performance of two working memory tasks: potential mechanisms of interference. Cereb Cortex 8:593–601

Klingberg T, O' Sullivan BT, Roland PE (1997) Bilateral activation of fronto-parietal networks by incrementing demand in a working memory task. Cereb Cortex 7:465–471.

Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, Miyashita Y (1998) Transient activation of inferior prefrontal cortex during cognitive set shifting. Nature Neurosci 1:80–84.

Kyllonen PC, Chrystal RE (1990) Reasoning ability is (little more than) working-memory capacity?! Intelligence 14:389–433.

Lauber EJ, Meyer DE, Evans JE, Koeppe RA (1997) Converging evidence from EEG and PET that prefrontal and superior parietal regions are involved in the executive control of task switching. Soc Neurosci Abstr 23:1120.

Morris RB (1996) Relationships and distinctions among the concepts of attention, memory, and executive function: a developmental perspective. In: Attention, memory, and executive function (Lyon GR, Krasnegor NA, eds), pp. 11–16. Baltimore, MD: Brookes.

Nagahama Y, Fukuyama H, Yamauchi H, Matsuzaki S, Konishi J, Shibasaki H, Kimura J (1996) Cerebral activation during performance of a card sorting test. Brain 119:1667–1675.

Norman DA, Shallice T (1986). Attention to action: willed and automatic control of behaviour. In: Consciousness and self-regulation (Schwartz GE, Shapiro D, eds), pp. 4. New York: Plenum Press.

Owen AM, Evans AC, Petrides M (1996) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cereb Cortex 6:31–38.

Parkin AJ (1998) The central executive does not exist. J Int Neuropsychol Soc 4:518–522.

Pennington BF, Bennetto L, McAleer O, Roberts RJ Jr. (1996) Executive functions and working memory: theoretical and measurement issues. In: Attention, memory, and executive function (Lyon GR, Krasnegor NA, eds), pp. 327–348. Baltimore MD: Brookes.

Prabhakaran V, Smith JAL, Desmond JE, Glover GH, Gabrieli JDE (1997)

Neural substrates of fluid reasoning: an fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. Cogn Psychol 33:43–63.

Price CJ, Moore CJ, Friston KJ (1997) Subtractions, conjunctions, and interactions in experimental design of activation studies. Hum Brain Map 5:264–272.

Rao SM, Bandettini PA, Binder JR, Bobholz JA, Hammeke TA, Stein EA, Hyde JS (1996) Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. J Cere Blood Flow Metab 16:1250–1254.

Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, Luxen A, Franck G (1996) Regional brain activity during working memory tasks. Brain 119:1617–1625.

Simon H (1969) The sciences of the artificial. Cambridge, MA: MIT Press.

Smith EE, Jonides J (1997) Working memory: a view from neuroimaging. Cogn Psychol 33:5–42.

Sternberg S (1969) Memory scanning: mental processes revealed by reaction-time processes. Am Scient 57: 421–457.

Suss H-M., Oberauer K, Wittmann WW, Wilhelm O, Schulze R (1996) Working memory capacity and intelligence: an integrative approach based on Brunswik symmetry. Technical report.

Talairach J, Tourneaux P (1988) Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical.

Weinberger DR, Berman KF (1996) Prefrontal function in schizophrenia: confound and controversies. Phil Trans R Soc Lond B351:1495–1503.

Wong EC, Boskamp E, Hyde JS (1992) A volume optimized quadrature elliptical endcap birdcage brain coil. Eleventh Annual Scientific Meeting, Society for Magnetic Resonance Medicine, Berlin, 4015.