

# Physiological Characteristics of Capacity Constraints in Working Memory as Revealed by Functional MRI

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**A fundamental characteristic of working memory is that its capacity to handle information is limited. While there have been many brain mapping studies of working memory, the physiological basis of its capacity limitation has not been explained. We identified characteristics of working memory capacity using functional magnetic resonance imaging (fMRI) in healthy subjects. Working memory capacity was studied using a parametric 'n-back' working memory task involving increasing cognitive load and ultimately decreasing task performance. Loci within dorsolateral prefrontal cortex (DLPFC) evinced exclusively an 'inverted-U' shaped neuro-physiological response from lowest to highest load, consistent with a capacity-constrained response. Regions outside of DLPFC, in contrast, were more heterogeneous in response and often showed early plateau or continuously increasing responses, which did not reflect capacity constraints. However, sporadic loci, including in the premotor cortex, thalamus and superior parietal lobule, also demonstrated putative capacity-constrained responses, perhaps arising as an upstream effect of DLPFC limitations or as part of a broader network-wide capacity limitation. These results demonstrate that regionally specific nodes within the working memory network are capacity-constrained in the physiological domain, providing a missing link in current explorations of the capacity characteristics of working memory.**

## Introduction

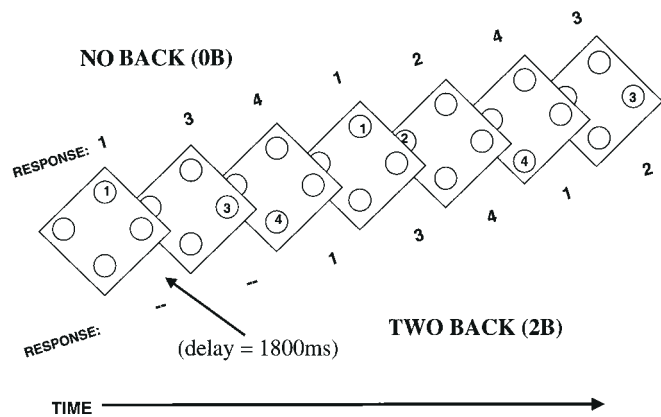
Working memory is a construct that describes the ability to transiently store and manipulate information on-line to be used for cognition or for behavioral guidance (Baddeley, 1986; Goldman-Rakic, 1996). A key aspect of working memory is its capacity limitation, usually reflected in cognitive testing as decreasing performance in response to increasing working memory load (Miller, 1956; Fuster, 1980; Shallice, 1988; Just and Carpenter, 1992). Numerous functional neuroimaging studies have used the spatial location and temporal characteristics of the 'activation' response during working memory to localize this cognitive phenomenon to regionally distinct components within a larger distributed network (Jonides *et al.*, 1993; Cohen *et al.*, 1994, 1997; McCarthy *et al.*, 1994; Braver *et al.*, 1997; Courtney *et al.*, 1997, 1998). For example, activation in dorsolateral prefrontal cortex [DLPFC; Brodmann's areas (BA) 9-10, 46] appears to be related to the active maintenance of information over a delay (Cohen *et al.*, 1997; Courtney *et al.*, 1997) and/or the manipulation of this information (Smith *et al.*, 1998). In contrast, activation in areas like the anterior cingulate is more the result of increased effort or task complexity (Pardo *et al.*, 1990; Barch *et al.*, 1997; Carter *et al.*, 1998). However, while previous functional neuroimaging studies have successfully characterized the 'where' of working memory, they have not addressed the dynamic range of physiological responses that presumably underlie variations in capacity.

Parametric working memory tasks, most notably the popular 'n-back' task (Gevins *et al.*, 1990), are ideally suited to examine

issues of dynamic range since working memory load can be increased incrementally during the same experiment. Prior *n*-back studies that specifically examined the relationship between working memory load and prefrontal cortical activation (for review, see Smith *et al.*, 1998) have demonstrated that increasing working memory load produces increasing brain activation, particularly in prefrontal cortex (Schumacher *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1997; Kammer *et al.*, 1997). This observation is difficult to reconcile with the notion of capacity limitation. However, in these earlier studies, accuracy (i.e. performance) tended to be held constant or remained high (e.g. >90%). Thus, working memory capacity was not likely exceeded nor was it directly measured. In addition, these versions of the *n*-back task probably utilized recognition more than recall memory, and thus these data may suggest that the recognition aspect of working memory may be less capacity constrained.

While few studies have directly addressed the physiology of capacity limitation, convergent findings from a wide variety of sources suggest that working memory capacity might arise from or be coincident with a failure to activate one or more key brain regions during working memory challenge. Studies in non-human primates using single-cell recording of prefrontal neurons and from human studies measuring evoked potentials during working memory have demonstrated reduced activation in behavior-specific loci coincident with behavioral error (Funahashi *et al.*, 1989, 1991; Gevins *et al.*, 1987). The prefrontal cortex has been reported to evince a plateau response at higher levels of memory load during a parametric verbal recall task (Grasby *et al.*, 1994). However, this task included both short-term (i.e. working memory) and long-term memory components, and thus these alterations in response could not be solely attributed to working memory capacity. Using a dual-task paradigm combining a complex reasoning task requiring working memory (Wisconsin Card Sorting Task) and an auditory shadowing task, Goldberg *et al.* (1998) found that prefrontal cortex responded to increasing cognitive workload with decreased activation.

Thus, one might expect that if capacity-limited physiological responses exist within the working memory network, they would be characterized by a declining response when behavioral measures of working memory (i.e. performance) indicate that capacity is being reached. Based on these considerations, we hypothesized the following: (i) some or all of load-sensitive loci within the working memory network would show capacity-constrained responses as defined by a peak and then decline in activation as working memory capacity was breached; and (ii) capacity-constrained responses would be prominent in DLPFC, consistent with its putative role as the 'central executive' node of working memory (Baddeley, 1986).



**Figure 1.** 'n'-back working memory task. The cognitive paradigm consisted of a novel version of the 'n'-back parametric working memory test organized in a traditional 'block' design. The 'no back' (0B) control task (upper figure) simply required the identification of the number currently seen. The working memory conditions required the encoding of currently seen numbers and the concurrent recall of numbers previously seen and retained over a delay (e.g. 'two back' or 2B, lower figure).

## Materials and Methods

### Subjects

We studied nine neurologically normal healthy controls (six male, three female; mean age = 29.3 years, range 18–39 years) utilizing blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) (Ogawa *et al.*, 1990; Bandettini *et al.*, 1992) and a graded working memory task – a variation of the *n*-back task (Gevins *et al.*, 1990) (Fig. 1). Volunteers were recruited from the staff of the National Institutes of Health. All subjects gave written, informed consent prior to participation.

The *n*-back task required subjects to continually update their mental set while responding to previously seen stimuli. Stimuli were presented via a fiber-optic goggle system (Resonance Technology, Van Nuys, CA). Responses were recorded via a fiber-optic response box with buttons arrayed in the same configuration as the stimuli presented on screen. 'n'-back refers to how far back in the sequence of stimuli that the subject had to recall. The stimuli consisted of numbers (1–4) shown in random sequence and displayed at the points of a diamond-shaped box. Working memory conditions were contrasted with an eyes-open rest condition and a non-memory guided control condition ('no-back' or 0B) that presented the same stimuli, but simply required subjects to identify the stimulus currently seen. As memory load increased, the task required the recollection of a stimulus seen one stimuli ('one back' or 1B), two stimuli ('two back' or 2B) or three stimuli ('three back' or 3B) previously (entailing delays of approximately 1.8, 3.6, or 5.4 s respectively) while continuing to encode additional incoming stimuli. Performance was recorded as percentage of correct responses (accuracy). Significant changes in performance were assessed using a repeated-measures analysis of variance (ANOVA) followed by Tukey's Honest Significant Difference (Tukey's HSD) *post-hoc*.

### Data Acquisition

BOLD fMRI data were collected on a standard 1.5 T General Electric Signa scanner (Milwaukee, WI) outfitted with a combined RF and gradient insert coil (Medical Advances, Milwaukee, WI) as previously described (interleaved,  $T_E = 60$  ms,  $T_R = 4$  s, flip = 90°, FOV = 24 mm, 64 × 64, voxel dimensions 3.75 mm isotropic) (Mattay *et al.*, 1996). fMRI data were co-registered with anatomical scans obtained during the same session for localization. To optimize subject tolerability, subjects were scanned in two different sessions. Three levels of the task (no-back, 1-back and 2-back, or no-back, 2-back and 3-back) were presented in 20 s epochs – counterbalanced and interspersed between an 'eyes open' rest state – with 9 blocks/session (8 epochs/block, 2 epochs/task/block). As an internal 'quality control' standard, this task required a continuous motor response (0.6 Hz), which reliably produces activation of contralateral

**Table 1**

Significant increases in activation as a function of working memory load

Area	Anatomy	Talairach coordinates
Right DLPFC (BA 46)	right middle frontal gyrus	-42 26 20
Right DLPFC (BA 46)	right middle frontal gyrus	-36 30 16
Right DLPFC (BA 45/47)	right inferior frontal gyrus	-30 32 0
Right PMC (BA 6/8)	right superior frontal gyrus	-28 14 48
Right PMC (BA 6/8)	right superior frontal gyrus	-20 8 56
Right PMC (BA 6/8)	right superior frontal gyrus	-32 4 52
Left DLPFC (BA 9)	left middle frontal gyrus	50 10 36
Left DLPFC (BA 45–46)	left inferior frontal gyrus	48 24 20
Left PMC (BA 6)	left superior frontal gyrus	32 0 56
Left SMA (BA 6)	left medial frontal gyrus	8 -2 64
Left SMA (BA 6)	left medial frontal gyrus	4 -8 68
Periculate (BA 6/32)	medial frontal gyrus	0 0 64
Right thalamus	right thalamus	-16 -4 12
Right thalamus	right thalamus	-2 -18 12
Right basal ganglia	right caudate	-8 -2 8
Right PAR (BA 39–40)	right inferior parietal lobule	-44 -28 32
Right PAR (BA 7)	right precuneus	-4 -60 60
Left PAR (BA 7/40)	left superior parietal lobule	36 -58 52

Areas and coordinates (x, y, z) correspond to the atlas of Talairach and Tournoux (1993). Brodmann's areas (BA) are given in parentheses. Data were maintained in radiological convention (R = L), therefore negative x coordinates refer to the right.

DLPFC, dorsolateral prefrontal cortex; BA, Brodmann's area(s); PMC, premotor cortex; SMA, supplementary motor area; PAR, parietal cortex.

sensorimotor cortex (left primary sensorimotor cortex) (Weinberger *et al.*, 1996; Callicott *et al.*, 1998). Ninety whole-brain fMRI volumes ('time points') were obtained per task condition (5 timepoints × 2 tasks/epoch × 9 blocks).

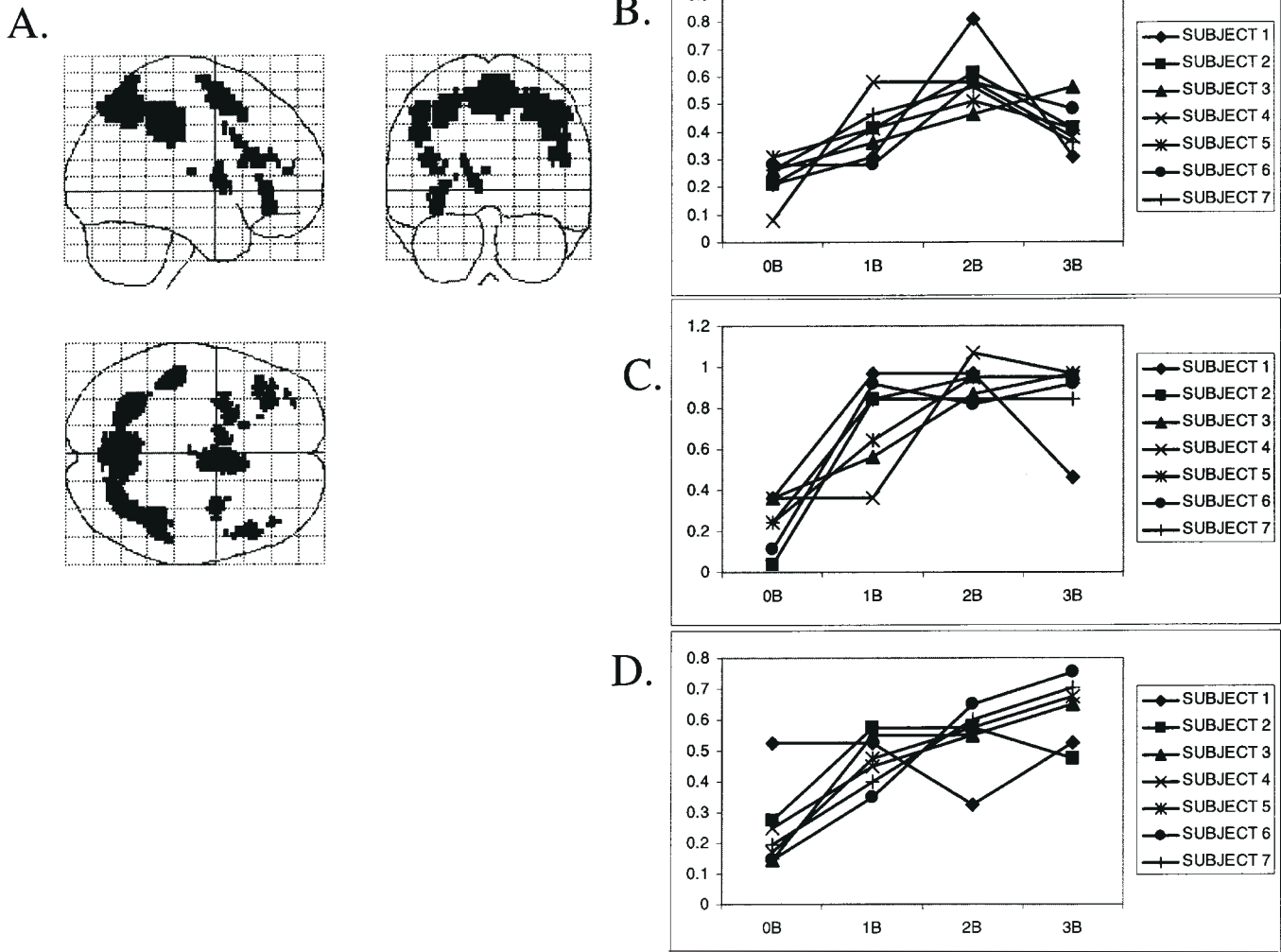
### Data analysis

We sought to identify those areas within brain responding to the graded manipulation of memory load (i.e. evincing a main effect of load) using a group analysis (Table 1, Fig. 2A). We then examined the patterns of fMRI signal change for each individual within these load-responsive loci (Fig. 2B–D). Specifically, we sought capacity-limited physiological responses as those that reacted differently to lower or subcapacity load (1B to 2B) and to higher or supracapacity load (2B to 3B).

Data sets were chosen for their high quality (scan stability) as demonstrated by both small motion correction (<2 voxels) and robust activation of the motor reference region (Callicott *et al.*, 1998). Most importantly, after motion correction, data between the two sessions were matched for voxel variance. Two of nine subjects were excluded on this basis. Seven subjects met these stringent criteria and were included for further analysis. Whole-brain fMRI volumes were registered using a sinc interpolation (Ostuni *et al.*, 1998) to the initial timepoint of the experiment after discarding the first timepoint of each epoch to account for the BOLD effect delay. To identify load-sensitive areas, individual whole-brain data were first stereotactically normalized to Talairach space using Automated Image Registration 3.0 (AIR 3.0) using a second-order polynomial warp model (Woods *et al.*, 1998a,b).

Voxel-wise signal intensities were ratio normalized to the whole brain mean and then detrended in a linear fashion with the baseline at each voxel set to 1000. Using SPM96, data were then smoothed with a Gaussian filter (10 × 10 × 10 mm) which was assumed to help control for inter-individual variance in regional activation. Data were analyzed using single-subject replication of conditions (0B, 1B, 2B and 3B) assuming a general linear model (Friston *et al.*, 1985). A group map (Fig. 2A) was computed wherein conditions for each individual were represented by mean scans comprising all repetitions of each task. We assumed independence of each mean observation since the first timepoint in each epoch was discarded to account for a delay in the onset of the BOLD response (Friston *et al.*, 1998).

The group map identified those voxels exhibiting a main effect of working memory load ( $P < 0.001$ , 2 voxel minimum cluster) (Fig. 2A). Within SPM96, *F* values were converted to *Z* scores, with larger *Z* values representing increasing effect size of memory load. The mean signal intensity changes for each individual subject across all levels of the task

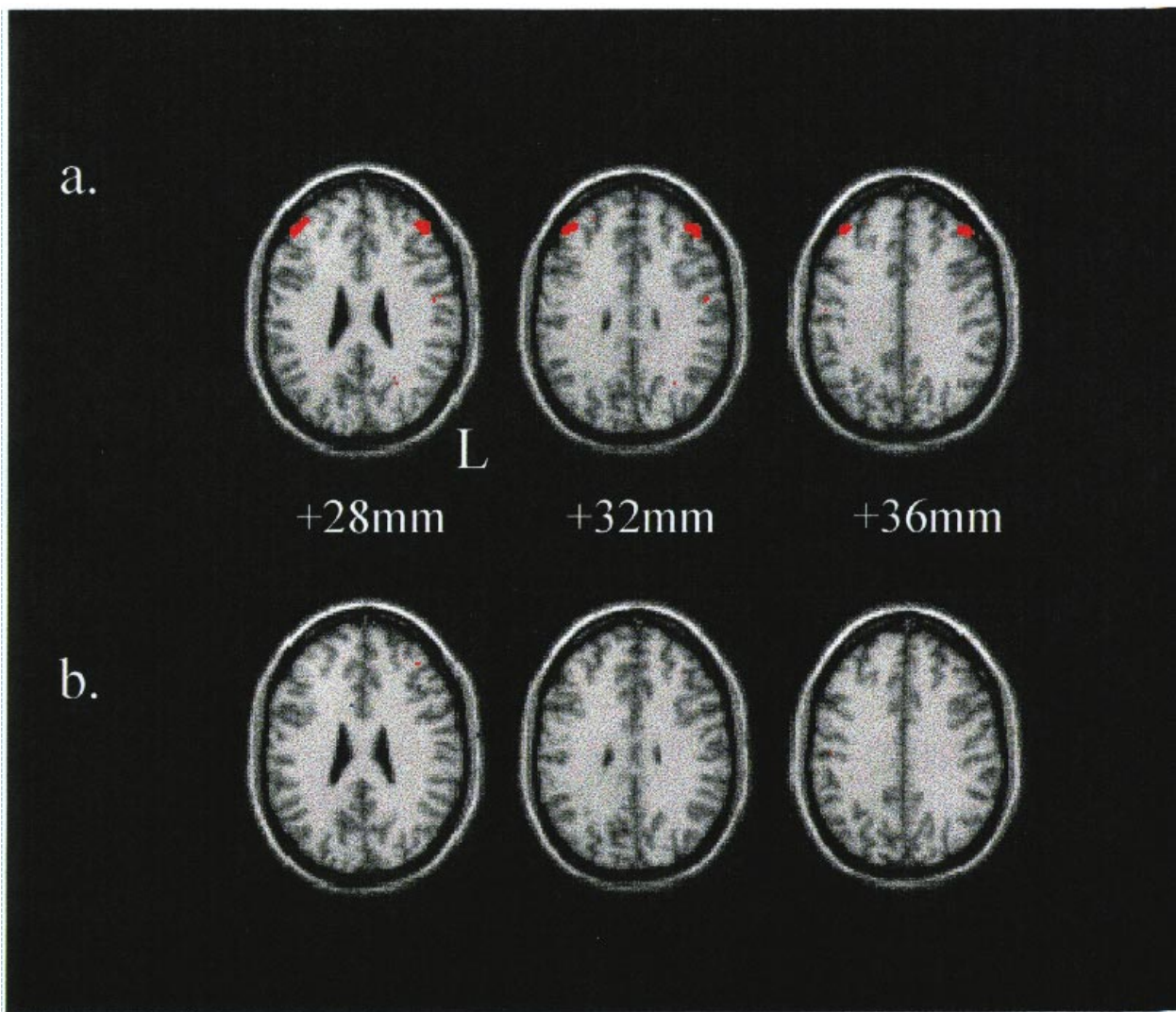


**Figure 2.** Group activation map and regional signal changes in response to increasing working memory load. (A) Group map showing regions with a significant response to changing working memory load presented in the sagittal, coronal, and transverse ‘look-through’ views. Data were maintained in radiological convention ( $R = L$ ). (B) Capacity-constrained response: left DLPFC (Talairach coordinate 48, 24, 20). The  $x$ -axis denotes increasing working memory load. The  $y$ -axis represents fMRI signal change as a percentage of rest. From 1B to 2B, 6/7 subjects increase fMRI signal, while 6/7 experience signal decrease from 2B to 3B ( $P = 0.01$ ). (C) Capacity-independent response: right precuneus ( $-4, -60, 60$ ). Most subjects (6/7) increase from 0B to 1B and stay the same from 1B to 3B (5/7). (D) Capacity-unconstrained response: medial periculate ( $0, 0, 64$ ). The majority of subjects evidenced continued linear increase in signal from 1B to 2B (5/7) and from 2B to 3B(6/7).

were then obtained at the locations indicated by the group map (local maxima). These values were expressed as a percentage of the mean value for rest at that voxel. Percentage change was obtained for each individual within significant loci at each level of memory load to produce the individual load–response graphs in Figure 2B–D (Braver *et al.*, 1997). Fisher’s exact tests were used *post-hoc* to assess the significance of the load–response curve patterns across levels of working memory load within (i.e. the number of individuals increasing or decreasing signal from 1B to 2B versus from 2B to 3B) and between all regional maxima (e.g. DLPFC versus parietal cortex). Finally, as a direct test of the relationship of task performance to BOLD fMRI activation in the DLPFC, we performed a voxel-wise correlation analysis between fMRI signal change and performance change as capacity was reached (i.e. between 2B and 3B). Mean fMRI signal change and mean performance were created for the 2B and 3B task for each individual. Then, the product moment correlation coefficient ( $r$ ) for the group was computed at each voxel. These values were then thresholded ( $r > 0.85$ ,  $P < 0.01$ ) and significant  $r$  values highlighted in red and displayed on a co-registered T1 template image (Fig. 3). Since this analysis was directed specifically at DLPFC, a correction for multiple statistical tests was not applied.

## Results

As expected, increasing working memory load was associated with declining accuracy (mean performance  $\pm$  standard deviation: 0B,  $99 \pm 3\%$ ; 1B,  $95 \pm 6\%$ ; 2B,  $88 \pm 15\%$ ; and 3B,  $81 \pm 23\%$ ). While performance tended to decrease as memory load increased [main effect of load  $F(df\ 3,18) = 4.05$ ,  $P = 0.02$ ], the decline was not statistically significant until three back (3B) (Tukey’s HSD  $P = 0.02$ ), implying a capacity limitation was being reached by 3B. Consistent with earlier studies utilizing this kind of task, we found load-sensitive responses in a distributed network that included DLPFC (BA 9–10/44–46), premotor cortex (lateral BA 6/8), a periculate region covering the medial frontal gyrus [supplementary motor area (medial BA 6) and anterior cingulate (BA 32)], the basal ganglia and thalamus, and parietal cortex (BA7, 39–40) (Table 1, Fig. 2). Although not specifically designed to address question of laterality or of dorsal versus ventral processing within DLPFC, we found bilateral DLPFC activation with a larger number of right DLPFC foci and



**Figure 3.** Capacity-dependent relationship between fMRI signal and performance. The product moment correlation coefficient ( $r$ ) between the mean fMRI signal and mean task performance for two back (2B) and three back (3B). These images were thresholded at  $r > 0.85$ ,  $P < 0.01$  (L = left, numbers refer to z coordinates in Talairach space). Significant voxels ( $r$  values) are highlighted in red. (a) fMRI signal in DLPFC was highly correlated with performance at 2B. (b) Past capacity, this relationship was all but lost at 3B.

both dorsal (BA 9/46) and ventral (BA6/8) areas active using our version of the  $n$ -back task.

Three different patterns of physiological responses within these key working memory-related regions were identified: signal increases in load-sensitive loci that peaked and declined as capacity was reached (i.e. 'capacity constrained'), loci that remained constant at all levels of load ('capacity independent'), and loci that continued to activate ('capacity unconstrained') (Fig. 2B–D respectively). Again, only the first or 'inverted-U' response was distinct in showing a change in slope from 1B to 2B and then from 2B to 3B. As noted above, these patterns were based on the proportion of individuals increasing versus decreasing fMRI signal in the transition from lower to higher load. As predicted, the majority of subjects demonstrated this inverted-U response across all load-sensitive voxels in DLPFC ( $P < 0.0001$ ), suggesting that a physiological capacity response was being reached within these loci. Furthermore, this inverted-U or capacity-constrained response was significantly

more frequent in individuals in DLPFC than in parietal cortex ( $P = 0.02$ ) or in other regions ( $P = 0.0008$ ).

Responses within the other cortical and subcortical regions were less homogenous. A similar inverted-U response pattern was found in two of the four loci within premotor cortex (Talairach coordinates  $-28, 14, 48$  and  $-20, 8, 56$ ), in one of the three loci within thalamus and basal ganglia ( $-16, -4, 12$ ), and in one of the parietal loci ( $36, -58, 52$ ) (all  $P < 0.05$ ). Two different response patterns were seen within parietal cortex. In contrast to left superior parietal lobule (i.e.  $36, -58, 52$ ), right inferior parietal lobule (BA 39–40) and right precuneus (BA 7) showed a binary early plateau or capacity-independent response (Fig. 2C) wherein activation failed to significantly change beyond 1B. Additionally, the medial pericuneus area encompassing BA 6,32 showed a continual linear increase in signal from 0B to 3B (Fig. 2D), suggesting a capacity unconstrained response. Finally, as a further illustration of the capacity-limited relationship between DLPFC activation and performance, we found that

activation within DLPFC (BA 9,10) was highly predictive of performance within capacity (i.e. 2B), but much less so beyond capacity (i.e. 3B) (Fig. 3).

## Discussion

Within the distributed network subserving working memory, there were both capacity-limited physiological responses, particularly prominent in DLPFC, and non-capacity constrained responses in nodes that behaved differently as capacity was exceeded, perhaps as subjects struggled to compensate for prefrontal limitations. Like other studies of working memory, we found activation in a network of regions, notably including prefrontal, premotor, periculate and parietal cortices. In contrast to other studies utilizing *n*-back tasks (Braver *et al.*, 1997; Cohen *et al.*, 1997; Smith *et al.*, 1998), we found that prefrontal cortical signal decreased at highest working memory load coincident with a significant decrement in performance (accuracy). There was heterogeneity of physiological response both within and across regions as found previously (Cohen *et al.*, 1997; Courtney *et al.*, 1997). The DLPFC and periculate were the most homogenous, exclusively evincing capacity-constrained and capacity-unconstrained responses respectively. Activation within DLPFC also had a unique relationship to performance across the range of working memory capacity tested herein (Fig. 3). At lower working memory load, there was a tight correlation between performance and activation. However, at higher load, this relationship broke down. Since subtraction maps of 3B-0B (data not shown) demonstrated DLPFC activation, these data suggest a diminution in efficiency at working memory load as capacity is approached. Clearly, at higher working memory load, activation is changing out of proportion to changes in performance.

Response within parietal cortex included capacity-independent nodes, perhaps indicating that some parietal loci were equally active during working memory irrespective of load, and thus were unlikely to represent capacity-constrained loci. Envisioned as subservient to the central executive in working memory, parietal cortex has been thought to serve as a working memory buffer for the perceptual attributes of task-related stimuli and thus might be expected to remain consistently active across all levels of load (Baddeley, 1986). While its exact function is unclear, the precuneus (BA 7) is thought to subservise memory retrieval, particularly as it relates to visual imagery (Fletcher *et al.*, 1997). As mentioned above, the periculate region showed a capacity-unconstrained response. As activation of this region has been associated with attention- and effort-related processes (particularly anterior cingulate) (Pardo *et al.*, 1990; Barch *et al.*, 1997; Carter *et al.*, 1998), this response may illustrate that such processes were not saturated by the demands of this particular task. It is intriguing to speculate whether capacity constraints arise in one key area (e.g. DLPFC) with functional implications elsewhere (e.g. the central executive node fails to recruit parietal cortex) or arise as a network-wide phenomenon. Furthermore, while we have emphasized the capacity-constrained responses in DLPFC, this response was found, albeit significantly less consistently, in the parietal cortex, premotor cortex and thalamus. Thus, the 'where' of capacity limitation for working memory may reside both within and outside of DLPFC. For example, one component of a capacity limitation might arise in the parietal buffer system. However, such details will need to be addressed in future studies designed to isolate both component functions of and various cortical nodes subservient to working memory. It is also

important to note that while there appears to be a significant decline in performance between 2B and 3B, this experiment was not designed to define in absolute quantitative terms the threshold of working memory capacity. The differences in working memory load between 1B, 2B and 3B are at best ordinal. Further, while we only found a significant decline in accuracy from 2B to 3B, our small sample size may have limited our ability to see a significant difference from 1B to 2B. This limits our ability to claim that working memory performance was absolutely breached at any particular level. However, it is interesting to note that our performance data are similar to those of Kammer *et al.* (1997), who also found significant performance differences only at 3B. Future work might focus on an expanded range with additional 'steps' in capacity to provide more 'points' on the load-response curve. We sought to contrast physiological responses associated with working memory performance that was well within and then clearly challenging capacity. It is interesting to note that while the magnitude of change in accuracy from 1B to 2B and 2B to 3B was similar (~7%), there were clear alterations in the patterns of activation within DLPFC and other capacity-constrained loci with the network from 2B to 3B. While we have suggested that these alterations in fMRI activation may be causally related to significant decrements in accuracy, these changes might arise from some uncoupling phenomena between vascular signal as measured by fMRI and neuronal firing. However, that such an uncoupling would occur only within select regions within the brain (e.g. DLPFC) while other regions continue to increase activation (e.g. periculate) over the same range of cognitive load seems unlikely unless, as we have suggested herein, these regions have a unique relationship to working memory capacity. As others have demonstrated (Luck and Vogel 1997; Goldberg *et al.*, 1998), the cognitive resources (e.g. neuronal activity) available for a given cognitive function like working memory are probably limited. Thus, anticipation and identification of fMRI response alterations at different portions of the cognitive load-response curve will be critical in the investigation of limitations in any cognitive function.

In comparing this study with previous functional neuroimaging studies of working memory, it is important to note that these earlier studies tended to control for accuracy. Since we were interested in capacity limitation, it was important to expand the range of our parametric design to include working memory load that began to exceed capacity (e.g. 3B) and produced significant decrements in accuracy. However, this approach invokes a long-standing criticism of neuroimaging studies that utilize tasks at which subjects perform below some arbitrary criterion for successful performance. One might suggest that activation maps beyond 2B unduly reflect 'poor performance' and thus do not address the question of capacity limitation *per se*. This explanation is problematic because it fails to explain stable fMRI signal in BA 7,40 and increasing signal in periculate cortex unless one evokes some complex 'willful' redirection of activity during periods of poor performance (for review, see Weinberger and Berman, 1996). Further, 3B performance ( $81 \pm 23\%$ ), even though significantly diminished compared to performance at lower working memory load, was still well above chance and the arbitrary cutoff for acceptable accuracy (e.g.  $>75\%$ ) used by other investigators (Braver *et al.*, 1997; Cohen *et al.*, 1997). That the load-response curve is an inverted-U in prefrontal cortex but continually increasing in the periculate region argues against the suggestion that pre-

frontal activation is related to active error detection (Barch *et al.*, 1997).

An alternative interpretation of these data is that prefrontal activation, rather than being related to working memory load *per se*, reflects differences in attention or willful action (Ingvar, 1994; Frith and Dolan, 1996) – also thought to be DLPFC functions. This ‘effortful attention’ hypothesis would predict increasing activation as working memory load increases, followed perhaps by decreasing activation as subjects become overwhelmed and subsequently disengage from the task. Again, this explanation cannot adequately explain the observation that fMRI signal remains constant in parietal cortex (BA 7,40) and increases in the periculate region from 2B to 3B, both counterintuitive to the idea of disengagement from the working memory task. Similarly, our performance data, which indicate that the percentage of omissions does not significantly increase from 1B to 3B [ $F(df\ 3,18) = 0.06, P = 0.9$ ], suggest that subjects were actively engaged and attending to the task throughout.

Many tasks (ours included) claim to measure the unitary phenomenon, ‘working memory’. While all involve holding information over a delay, they all probably differ in the relative amount of other component processes (e.g. encoding, recognition, manipulation, inhibition or forgetting). In this sense, our version of the *n*-back task was probably particularly demanding on the encoding and forgetting (i.e. shuttling information and managing interference) aspects of ‘working memory’ in addition to remembering – and by inference may have entailed greater cognitive workload than recognition-type delayed memory tasks. Thus, comparison across different working memory tasks, even versions of the *n*-back task, must be undertaken with caution. For example, other versions of the *n*-back task usually include a lower number of target matches (e.g. 30% target), whereas our version of the *n*-back task required matches for every stimulus (100% target). Also, the control task (no back) in our experiment, in which subjects encode and respond to each changing stimulus, differs from other versions which require subjects to scan incoming stimuli for a prearranged target and thus involves some recognition memory (Cohen *et al.*, 1997; Smith *et al.*, 1998). Thus, in general, we are cautious in attributing the coincident decline in activation and behavioral performance solely to any one particular component of ‘working memory’.

Given the possibility of increased or at least different cognitive workload in our version of the *n*-back task, we may have been more likely to find decreasing activation at higher working memory load than previously (Braver *et al.*, 1997; Smith *et al.*, 1998). However, even though the goal of this study was to observe changes in the fMRI activation response to parametric variations of a working memory task (i.e. a ‘within task’ question), our results should be reproducible with versions of the *n*-back task or other working memory tasks provided that they can be parametrically manipulated within a given experiment to the point that individuals approach or exceed their capacity to perform that task accurately. One potential disadvantage of this approach is that driving individuals too far into inaccuracy (e.g. 4B or 5B) might introduce unnecessary complexity into the interpretation of resultant brain maps since individuals might struggle with and perhaps disengage from the task. In general, the physiological mechanism for reduced activation (as opposed to sustained or increasing activation) in cortical loci as capacity is breached remains unclear. Our data are consistent with studies that have demonstrated reduced activation in behavior-specific loci coincident with behavioral

error or increased cognitive workload (Gevins *et al.*, 1987; Funahashi *et al.*, 1989, 1991; Goldberg *et al.*, 1998). Furthermore, the capacity-limited fMRI response within DLPFC to increasing working memory load has been replicated in two additional cohorts of healthy controls during the placebo arms of infusion studies using ketamine (Bertolino *et al.*, 1997) and amphetamine (Mattay *et al.*, 1997). In these studies, loci within DLPFC also peaked at 2B.

While the variables determining an individual’s working memory capacity are probably numerous, individual capacity may have larger implications for other higher cortical functions, including intelligence, because working memory is thought to be a key component of such functions (Daneman and Carpenter, 1980). Individual differences in working memory capacity may also be important in understanding neuropsychiatric disorders, such as schizophrenia, in which physiological dysfunction of regions like DLPFC probably underlie the inability to muster the necessary physiological response to working memory demands (Weinberger, 1995; Stone *et al.*, 1998). Using an *n*-back task, we have shown that patients with schizophrenia who consistently perform worse than controls on the 2B task show a pattern of response within DLPFC that includes loci that plateau at 1B, again suggesting their performance failures stem from limited working memory capacity perhaps arising from inherent DLPFC dysfunction (Weinberger *et al.*, 1997). Our observation that certain loci within the working memory network appear limited in their fMRI activation response to increasing memory load may provide a missing link between the ‘where’ of working memory and the ‘how’ of capacity limitations. This missing link may also allow for a more thorough exploration of the biological factors that determine variations in these responses and in cognitive performance across individuals.

## Notes

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