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Temporal dynamics of brain activation during a working memory task

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Working memory is responsible for the short-term storage and online manipulation of information necessary for higher cognitive functions, such as language, planning and problem-solving[1,2]. Traditionally, working memory has been divided into two types of processes: executive control (governing the encoding manipulation and retrieval of information in working memory) and active maintenance (keeping information available 'online'). It has also been proposed that these two types of processes may be subserved by distinct cortical structures, with the prefrontal cortex housing the executive control processes, and more posterior regions housing the content-specific buffers (for example verbal versus visuospatial) responsible for active maintenance[3,4]. However, studies in non-human primates suggest that dorsolateral regions of the prefrontal cortex may also be involved in active maintenance[5-8]. We have used functional magnetic resonance imaging to examine brain activation in human subjects during performance of a working memory task. We used the temporal resolution of this technique to examine the dynamics of regional activation, and to show that prefrontal cortex along with parietal cortex appears to play a role in active maintenance.

Neurologically normal subjects (5 males, 5 females; ages 18–34) were scanned while performing a sequential-letter memory task (Fig. 1). This task has reliably produced activation of cortical regions that are believed to be involved in working memory.[9,10] Memory load was varied parametrically to identify these regions sensitively[11]. In addition, the rate of stimulus presentation was slowed in order to acquire multiple scans during each trial, and thereby track the dynamics of activation (Fig. 2). We reasoned that temporal information, together with the manipulation of memory load, would provide new information permitting a finer analysis of the cognitive functions associated with activated regions than has previously been possible. Specifically, we predicted that sensory and motor processes (ones not involved in working memory) would exhibit transient increases in activation associated with stimulus presentation and response execution (peaking after a delay of about 5 s, as a result of the well-characterized lag in haemodynamic response[12-14]), but should not vary as a function of memory load. We predicted that the areas involved in working memory would vary as a function of memory load, with greater activation at higher levels of load. Furthermore, we predicted that such load-sensitive areas would dissociate into two types: those involved in active maintenance would exhibit sustained activation throughout the trial, whereas those involved in other working memory functions (assumed to be time-limited, such as updating working memory contents, decision processes and so on) would exhibit transient activation (such as sensory and motor processes) but would peak higher (or last longer) at higher levels of load. Thus these areas would show an interaction between the effects of time and load.

Our findings, from pooled data for 10 right-handed subjects, reveal each of the patterns predicted above (Fig. 3). As expected, regions within visual, motor and somatosensory cortex all exhibit strong effects of time, but no effect of memory load (see Table 1 and Fig. 3a). Motor and somatosensory regions are left-lateralized, consistent with right-handed response. The time course of activation in all of these regions concurs with other studies focusing specifically on these systems[12,13] and validates our ability to track the dynamics of activation using this method.

The distribution of regions showing sensitivity to memory load corresponds well with previous observations using this task[10,11] and with structures thought to be involved in working memory. These include dorsolateral prefrontal cortex (PFC), more posterior and inferior regions of frontal cortex (including Broca's area), and posterior parietal cortex. As predicted, however, two different temporal patterns are evident among these regions. Within anterior frontal cortex, including dorsolateral PFC (BA46/9), only regions showing an effect of load are observed but none showing an interaction with time (Table 1 and Fig. 3b). Such regions are also observed within more posterior structures, including Broca's area (BA44) and posterior parietal cortex (BA40), but in posterior areas they co-occur with (and sometimes are directly adjacent to) other regions that show an interaction between load and time (Fig. 3c).

The pattern of activation observed within dorsolateral PFC (greater with higher levels of load, and sustained throughout the trial) is consistent with a role in the active maintenance of information in working memory. This suggests that PFC is not exclusively

involved in transient processes, such as assigning temporal order, updating the contents of working memory, or other memory-related processes (such as encoding or retrieval from longer-term stores[15]). Previous neuroimaging studies have found PFC activation during the retention interval of a working memory task, but lacked the temporal resolution to determine whether such activation was sustained throughout the entire retention interval, or occurred only transiently (early or late) during the interval[16]. However, our findings are consistent with those of a study of working memory for faces also reported in this issue[17].

One possible concern might be that the processes within dorso-lateral PFC were transient, but lasted somewhat longer than sensory or motor-related processes. This might have produced a more prolonged haemodynamic response that did not have time to recover within the 10-s period between stimuli (see Methods), and thus would appear as a sustained response. To address this concern, we conducted a small supplemental study using the same task, but with a 20-s delay to allow for recovery of the haemo-dynamic response. We observed sustained elevation of the func-tional magnetic resonance imaging (fMRI) signal within dorsolateral PFC even with this longer delay, consistent with our interpretation of processing that endures over the delay within this brain region.

The effect of load in PFC appears as a step function, with activation increasing primarily between the 1- and 2-back condi-tions (see legend to Fig. 1). Similar observations have been made in a positron emission tomography (PET) study using this task[18]. How-ever, in at least one other study we have observed a more gradual (linear) increase of PFC activation across levels of load[11], and in the current study a similar graded pattern was observed within the areas of parietal cortex showing an effect of load. At present, we do not fully understand these discrepancies, although the step pattern observed within PFC may be related to the fact that the 2- and 3-back conditions depend on maintenance of information about the

Table 1 Regions exhibiting significant task-related activity

| Region (Brodmann's area)	Talairach coordinates (x, y, z)	Statistical effect (Max z-value)
Prefrontal cortex		
R middle frontal Gyrus (BA9/46)	37 32 30	Load (3.82)
R superior frontal gyrus (BA8)	7 29 37	Load (3.52)
L, R inferior frontal gyrus (BA44)	− 41 8 16, 45 13 26	Load (4.26, 3.15)
L interior frontal gyrus (BA44)	− 43 8 26	Load × time (4.91)
Cingulate cortex		
Anterior cingulate (BA32)	0 5 40	Time (5.61)
	0 16 43	Load × time (2.93)
Insular cortex		
L, R frontal operculum	− 29 17 1, 32 22 4	Time (4.02, 3.72)
Motor and somatosensory cortex		
L, R middle frontal gyrus (BA6)	− 35 2 40, 32 6 58	Load (3.01, 4.12)
R Middle frontal gyrus (BA6)	46 5 45	Load × time (2.87)
L, R middle frontal gyrus (BA6)	− 26 − 4 56, 31 − 1 54	Load × time (3.09, 3.03)
L precentral gyrus (BA6)	− 45 − 4 42	Load × time (2.45)
L precentral gyrus (BA4)	− 35 − 15 55	Time (5.20)
L postcentral gyrus (BA1/2/3)	− 45 − 25 57	Time (4.75)
Parietal cortex		
R superior parietal lobule (BA7)	12 − 61 53	Load (3.37)
L, R supramarginal gyrus (BA40)	− 40 − 48 40, 44 − 55 43	Load (3.72, 3.75)
L, R supramarginal gyrus (BA40)	− 28 − 41 41, 37 − 44 39	Load × time (3.26, 4.34)
Temporal cortex		Time (3/41)
R superior temporal gyrus (BA22)	64, − 28 14	
Visual cortex		
L precuneus (BA18)	− 20 − 66 29	Time (3.34)
L, R cuneus/lingual gyrus (BA17/18)	− 9 63 4, 7 − 60 4	Time (3.96, 4.05)
L middle occipital gyrus (BA19)	− 37 − 60 − 3	Time (3.21)
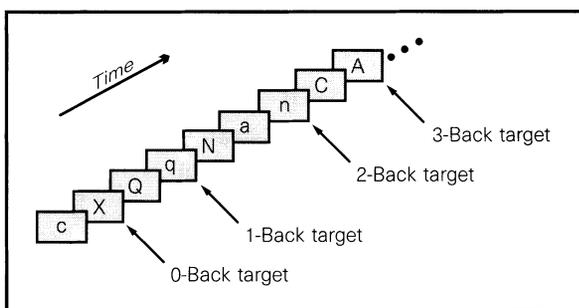
Figure 1 The four memory conditions of the sequential letter ('n-back') task. In the 0-back conditions, subjects responded to a single pre-specified target (such as X). In the '1-back' condition, the target was any letter identical to the one immediately preceding it (one trial back). In the 2-back and 3-back conditions, the target was any letter identical to the one presented 2 or 3 trials back, respectively. Thus, working memory load increased from the 0-back to the 3-back conditions. All other task parameters were the same across all conditions.
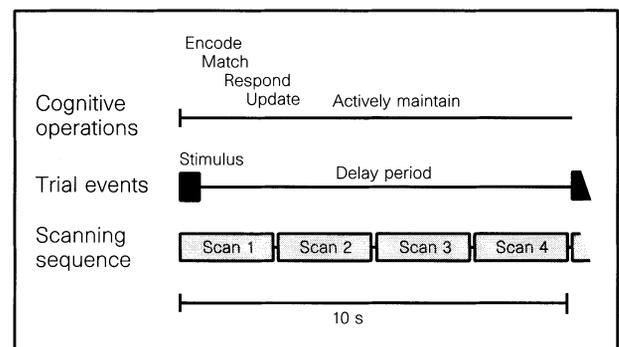

Figure 2 Diagram of the experimental protocol, showing the sequence of stimulus events and scan acquisition during a single trial, as well as the approximate time course of mental operations presumed to be engaged by the task.

sequential order of stimuli, whereas the 0- and 1-back conditions do not.

The finding of sustained activation within dorsolateral PFC challenges the strong view that there is a clean dissociation between executive and maintenance processes, with PFC housing the former but not the latter. At the very least it suggests that the relationship between executive functions and active maintenance may be more complex than originally thought. For example, recent computational theories[2,19] suggest that PFC may contribute to executive control by actively maintaining particular types of information (such as goal or other context representations that bias processing in posterior systems, or the sequential relationships between stimuli), or that it may be required for active maintenance under particular circumstances (such as in the presence of distracting information[20]). These possibilities are also consistent with recent neurophysiological findings of sustained activity of neurons within the PFC of non-human primates in delayed response tasks[5,6], some of which have specifically involved the maintenance of sequential order information[7,21] and distractor stimuli[8]. Thus, a characterization of the type of information that is actively maintained or the conditions under which maintenance is required may be more relevant to the function of PFC than a distinction between active maintenance and executive control.

Alternatively, PFC may not be a site of active storage but may still play an adjunct role by issuing periodic control signals that continue to engage more posterior systems in which information is actively maintained. If the control signal were generated sufficiently often (and more so at higher levels of load), it might produce a pattern of sustained, load-sensitive activation within PFC as measured by fMRI. Thus, differing views regarding the role that PFC plays in active maintenance may be consistent with the pattern of dorsolateral PFC activation observed in our study. However, these views make different claims about whether or not task-specific information is actually maintained within PFC. An adjudication of this issue will require more detailed data than has been provided by human neuroimaging studies to date.

A different possibility is that sustained activation within PFC reflects the operation of more general processes associated with task difficulty and mental effort, rather than processes specific to working memory. We examined this possibility in another recently
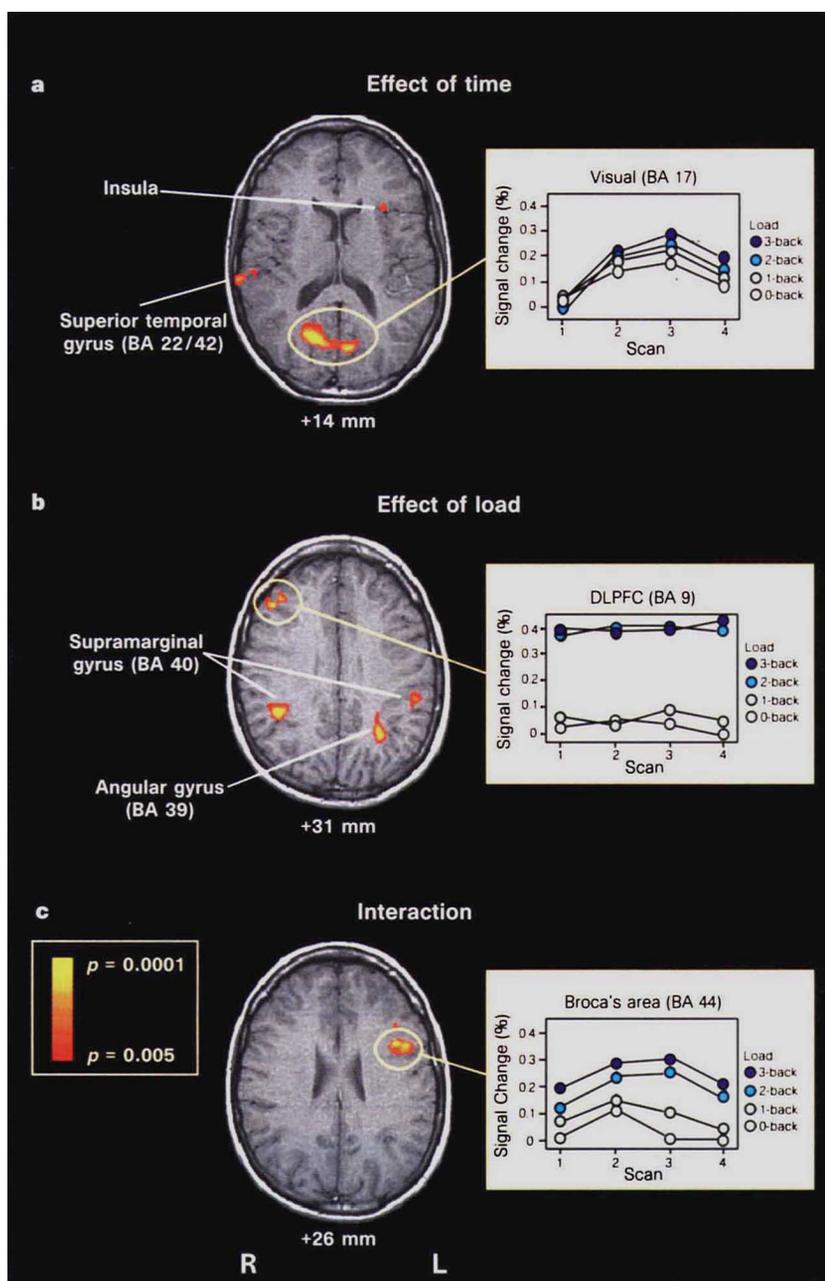

Figure 3 Images showing regions of activation representative of each effect. Insets plot the signal for the pixel showing the strongest effect in the designated region, as a proportion of the lowest value of that pixel across scans and load conditions. **a**, Effect of time; **b**, effect of load; **c**, Interaction between time and load.

completed experiment[22], in which memory and task difficulty were independently manipulated. Dorsolateral PFC was activated in memory-demanding conditions (showing a similar sustained pattern), but not in other conditions that relied significantly less on active maintenance but were more difficult (for example, stimulus degradation). Thus, activation of this structure seems to reflect processes specific to working memory, and not processes associated more generally with task difficulty.

Apart from the dorsolateral PFC, sensitivity to load was observed primarily in posterior regions of frontal cortex (including Broca's area), and in posterior parietal cortex. These areas may participate with dorsolateral PFC in the active maintenance of information within working memory[10,23]. However, unlike dorsolateral PFC, some of these structures exhibited additional regions of activation characterized by an interaction of load and time. All of the latter showed transient activation that was greater and more prolonged as load increased, similar to the pattern shown in the inset for Fig. 3c. These systems may play a role in transient working memory processes, such as the updating of contents, comparison operations and possibly rehearsal. The last of these is of particular interest with regard to the pattern of activation observed in Broca's area (left BA44; see Fig. 3c), considering the role that this region is thought to play in articulatory rehearsal[3,4,23,24]. Rehearsal is usually assumed to be an ongoing process, suggesting that we should have observed a pattern of continuous activation in Broca's area. However, introspective reports from the subjects suggest that they may have stopped rehearsal early in the delay in the lower-load conditions of our experiment. This would be consistent with the observation of transient activation at lower loads and more prolonged activation at higher loads. This interpretation requires further examination. Nevertheless, the pattern of activation observed within Broca's area is distinct from the one observed in dorsolateral PFC, and raises the possibility of a dissociation between the processes underlying explicit verbal rehearsal, and other mechanisms for actively maintaining information that may reside within dorsolateral PFC. □

Methods

Cognitive task. Stimuli were pseudorandom sequences of 14 consonants, presented visually (500 ms duration, 9,740 ms interstimulus interval) using a Macintosh computer and PsyScope software[25]. The 10 s trial duration was chosen to allow sufficient time for the MR signal to return to baseline between trials for stimulus-locked events[12,13] and to permit acquisition of fMRI data over four time periods during each trial (see Fig. 2). Subjects used their dominant hand to respond to each stimulus, by pressing one button for targets (33% of trials) and another for non-targets. Only subjects who demonstrated acceptable accuracy (>75%) on all conditions during a pretesting session were scanned. During scanning, average accuracy across conditions was 90% for target trials and 98% for non-target trials, which is comparable to previous studies using trials of shorter duration. The task was administered in blocks of 14 trials at constant load level, during which scanning occurred (see Fig. 2). Six blocks were run for each of the four levels of load, pseudo randomly ordered (with the constraint that each level was sampled once every four blocks), to control for confounding effects of time on task, head movement and scanner drift.

Image acquisition. Scanning took place in a conventional 1.5T GE Signa whole-body and standard RF coil scanner in the UPMC MR Research Center. Twenty-four slices (3.75 mm³ isotropic voxels) were acquired parallel to the AC–PC line. Functional scans, T2* weighted for maximum sensitivity to variations in oxygen-saturation[14,26] were acquired using a 4-interleave spiral-scan pulse sequence[27] (TR 640 ms, TE 35 ms, flip angle 40°, FOV 24 cm). This allowed 8 slices to be acquired every 2.5 s. Scanning was synchronized with stimulus presentation so that a set of 8 slices was acquired four times during each 10 s trial. The same set of 8 slices was scanned for three consecutive trials, followed by a different set of 8 slice locations. Set order was counterbalanced across blocks to control for asynchronous acquisitions across regions. Scanning occurred during only 9 of the 14 trials in each block, with the remainder used to load working memory and allow the fMRI signal to achieve steady state. Nine trials per block × 6 blocks per condition divided by 3 scan sets per whole brain

yielded a total of 18 scans in each slice plane (1–24) for each time point (1–4) at each level of load (0–3). Following functional scanning, a high-resolution structural scan was performed in the same planes as the functional scan for anatomic localization and coregistration of images across subjects (discussed below).

Image analysis. Before analysis, images for all subjects were coregistered to a common reference brain, using a 12-parameter automated algorithm (AIR[28]), and then smoothed using a three-dimensional gaussian filter (8 mm FWHM) to accommodate between-subject differences in anatomy. This approach to pooling data across subjects is used frequently in PET studies to increase statistical power and permit quantitative identification of regions that activate reliably across subjects. We have used this approach successfully in a previous fMRI study[11]. Planned contrasts were used to identify pixels showing any one of the following three effects ($P < 0.005$): (1) monotonic increase in signal as a function of load; (2) transient increase in signal over time, greater during scans 2 and 3 of each trial than scans 1 and 4; or (3) a combination of these effects that manifested as a significant interaction of time and load (determined using a 2-way ANOVA followed by the contrasts described for both of the first two effects). The second of these contrasts (used to identify transient increases associated with stimulus and response-locked events) takes into account the expected 5 s lag in the fMRI response, based on observations that we and others have made regarding the time course of the fMRI signal in response to brief events[12,13] Images were formed for each of the three effects that included pixels significant only for the corresponding effect. Regions made up of 8 or more contiguous pixels were then identified in each of these images (as a precaution against type I errors[29], and insuring an effective pixel-wise alpha of $P < 0.005$). Finally, these regions were overlaid onto the reference structural images (to determine their anatomic location), which were then transformed to standard stereotactic space using AFNI software[30].

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Transient and sustained activity in a distributed neural system for human working memory

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Working memory involves the short-term maintenance of an active representation of information so that it is available for further processing. Visual working memory tasks, in which subjects retain the memory of a stimulus over brief delays, require both the perceptual encoding of the stimulus and the subsequent maintenance of its representation after the stimulus is removed from view. Such tasks activate multiple areas in visual and prefrontal cortices[1-9]. To delineate the roles these areas play in perception and working memory maintenance, we used functional magnetic resonance imaging (fMRI) to obtain dynamic measures of neural activity related to different components of a face working memory task—non-selective transient responses to visual stimuli, selective transient responses to faces, and sustained responses over memory delays. Three occipitotemporal areas in the ventral object vision pathway had mostly transient responses to stimuli, indicating their predominant role in perceptual processing, whereas three prefrontal areas demonstrated sustained activity over memory delays, indicating their predominant role in working memory. This distinction, however, was not absolute. Additionally, the visual areas demonstrated different degrees of selectivity, and the prefrontal areas demonstrated different strengths of sustained activity, revealing a continuum of functional specialization, from occipital through multiple prefrontal areas, regarding each area's relative contribution to perceptual and mnemonic processing.

Imaging studies in humans have shown that both visual and prefrontal cortices are active during visual working memory tasks, but these studies did not have sufficient temporal resolution to distinguish transient activity during stimulus presentation from sustained activity after the stimulus is removed from view[1-9]. Increases in activity in visual and prefrontal cortices could therefore be attributed either to attentional enhancement of responses to stimuli, or to working memory, or to both. By contrast, electrophysiological studies in humans, which do have sufficient temporal resolution to distinguish transient from sustained activity, have not had sufficient spatial resolution to attribute the sources of these signals to specific anatomical locations[10,11]. We used fMRI to measure changes in neural activity over the course of a working memory task in order to distinguish the perceptual and mnemonic roles played by the cortical regions that participate in visual working memory (see also ref. 12).

Functional MRI scans were obtained while eight subjects alternately performed working memory and sensorimotor control tasks (Fig. 1; and see Methods). Six bilateral regions were identified that were consistently activated across subjects (Tables 1 and 2). The temporal responses of these regions were analysed using multiple regression with regressors related to three different cognitive components of the task: (1) a transient, non-selective response to visual stimulation that was equivalent for faces and scrambled faces; (2) a transient, selective response to faces; and (3) a sustained response over memory delays (Figs 1–3; and see Methods). Because complex objects other than faces were not used as stimuli, the transient, selective response to faces could indicate either face-selectivity *per se* or selectivity for any meaningful visual stimulus. Similarly, a sustained response over memory delays could indicate either a working memory system that is specific to faces, or a generic visual object working memory system.

All subjects showed activity in ventral occipitotemporal extrastriate visual areas that was correlated with stimulus presentation. A region in the posterior lingual and fusiform gyri, Brodmann area (BA) 18, showed a transient, mostly non-selective response to stimuli (Fig. 2a). In half of the subjects, the response to faces in this region was significantly greater than the response to scrambled faces, but the magnitude of this difference was small. Rostral to this relatively non-selective area, a ventral temporal region in the mid-to-anterior fusiform gyrus (BA 37) showed a transient, more face-selective response with a small, but significant, level of sustained activity during the memory delay. This pattern of activation indicates that the anterior fusiform gyrus is involved to a greater extent in the perceptual processing of faces than is the more posterior region and may also be involved in the maintenance of an active representation of the face during the memory delay (Fig. 2b). Face-selective responses, similar to the responses in the anterior fusiform gyrus, were also seen in the inferior occipital sulcus (BA 18/19), an area more lateral and more posterior than the fusiform face-selective area. The activity in the inferior occipital sulcus was more sustained during the memory delay than was the activity in the anterior fusiform gyrus, but the regression weights for non-selective and face-selective responses to stimuli in these regions were approximately the same.

Three distinct prefrontal areas were identified that all showed sustained activity during the memory delay interval: one in the posterior middle and inferior frontal gyri (BA 9/44), a second in the inferior frontal gyrus near the anterior end of the insula (BA 45/47), and a third in the anterior middle frontal gyrus (BA 46) (Table 2; Figs 2c–e and 3). The contribution of the memory delay regressor was significant for all three of these areas, but the relative magnitudes of the regression weights were different, indicating that the functional responses for these regions differed. The posterior middle frontal gyrus area had the most non-selective visual stimulation activity and the least memory delay activity, whereas the anterior middle frontal area had the least non-selective visual stimulation activity and the most memory delay activity. Regression weights for the posterior middle frontal gyrus differed significantly from those for the other two prefrontal areas ($F(1, 111) = 27.91$, $P < 0.0001$). Although the difference between the weights for the inferior frontal and anterior middle frontal areas did not reach significance ($P = 0.054$), their anatomical segregation clearly identified them as distinct regions.

There was a systematic progression in the relative strengths of perception- and memory-related activity from posterior extrastriate through prefrontal areas, indicating that this distributed neural system for working memory is hierarchically organized (Fig. 3). In the extrastriate visual areas, the progression from mainly non-selective perceptual to face-selective perceptual activity is consistent with the well established hierarchical organization of visual cortex[13]. Progressive changes in perception- and memory-related activity in the prefrontal areas suggest that these areas, like those in extrastriate