Distributed and Associative Working Memory

This study explores the cortical cell dynamics of unimodal and cross-modal working memory (WM). Neuronal activity was recorded from parietal areas of monkeys performing delayed match-to-sample tasks with tactile or visual samples. Tactile memoranda (haptic samples) consisted of rods with differing surface features (texture or orientation of ridges) perceived by active touch. Visual memoranda (icons) consisted of striped patterns of differing orientation. In a haptic–haptic task, the animal had to retain through a period of delay the surface feature of the sample rod to select a rod that matched it. In a visual–haptic task, the animal had to retain the icon for the haptic choice of a rod with ridges of the same orientation as the icon’s stripes. Units in all areas responded with firing change to one or more task events. Also in all areas, cells responded differently to different sample memoranda. Differential sample coherent firing was present in most areas during the memory period (delay). It is concluded that neurons in somatosensory and association areas of parietal cortex participate in broad networks that represent various task events and stimuli (auditory, motor, proprioceptive, tactile, and visual). Neurons in the same networks take part in retaining in WM the memorandum for each trial, whether it is encoded haptically or visually. The VH association by parietal cells in WM is analogous to the auditory–visual association previously observed in prefrontal cortex. Both illustrate the capacity of cortical neurons to associate sensory information across time and across modalities in accord with the rules of a behavioral task.

Keywords: cross-modal, haptic, monkey, network, parietal cortex, units

Introduction

It is generally accepted that working memory (WM) is supported by a category of cortical neurons, probably pyramidal cells, that undergo persistent activation during the memorization of a sensory stimulus for the performance of a motor act contingent on that stimulus. Such cells, dubbed “memory cells,” were first found and intensively examined in the prefrontal cortex of monkeys performing delay tasks (Fuster and Alexander 1971; Niki 1974; Funahashi et al. 1989; Miller et al. 1996; Romo et al. 1999; Takeda and Funahashi 2002). In these tasks—for example, delayed response and delayed matching—the stimulus and the act are separated by a delay, ranging from hundreds of milliseconds to tens of seconds, that forces the animal to retain the stimulus (memorandum) in WM. By definition, the discharge of memory cells is higher during that delay, in the mnemonic retention of the stimulus, than during baseline periods between trials, when the animal does not need to retain any particular stimulus. Memory cells are also present in inferotemporal cortex (Fuster and Jervey 1982; Miyashita and Chang 1988; Miller et al. 1993), posterior parietal cortex (Gnadt and Andersen 1988; Mazzoni et al. 1996), and anterior parietal cortex (Koch and Fuster 1989; Zhou and Fuster 1996; Romo and Salinas 1999), where they engage in the retention of visual, spatial, and tactile information, respectively.

From the available knowledge of the properties and location of memory cells, the concept emerged of a distributed cortical system to support the cognitive function of WM, as postulated by Baddeley (1983) at the core of what he called the “central executive.” WM would be a specialized mnemonic function served by a dedicated system of cells and connections in which the prefrontal cortex would play a crucial role. However, whereas the general idea of distributed WM under some form of prefrontal control is now well established by single unit and imaging data (Fuster et al. 1985; Postle and D’Esposito 1999; Chafee and Goldman-Rakic 2000; Duncan and Owen 2000; Miller 2000; Fuster 2001), the idea of WM as a distinct form of short-term memory with a dedicated brain system appears increasingly implausible. Instead, WM seems to rely largely on the temporary activation of updated old memory for the attainment of a cognitive or behavioral goal in the proximate future (Crowder 1993; Ericsson and Kintsch 1995; Cowan 1988; Fuster 1999; Curtis and D’Esposito 2003; Ruchkin et al. 2003).

Careful review of the relevant literature reveals that the excitatory activity of cortical memory cells is rarely tuned exclusively to the particular sensory feature of the cue or memorandum that the animal must remember through the delay period of a delay task. Sharp or reciprocal sensory tuning (e.g., excitation by one cue and inhibition by another) is seldom observed (Fuster and Jervey 1982; Funahashi et al. 1989; Romo et al. 1999). Much more commonly, a cell will be excited (some cells are inhibited) by the 2 or more memoranda that the animal successively uses in its task, though ordinarily more by one than by the other. Even in primary somatosensory (Zhou and Fuster 1996) or visual (Supér et al. 2001) cortex, memory cells are not sharply tuned to a given memorandum but, instead, modulated to different firing frequencies by different memoranda. A basic common level of excitatory response to several stimuli, that is, the different memoranda, indicates that those cells relate to common stimulus properties (e.g., position, brightness, association with motion, and reward), not just to a given trial-specific property to be retained in WM (red, green, right, left, etc.). Supposedly, some of those common stimulus properties eliciting a base level of neuronal excitation have been associated with one another in the learning of the WM task. Further evidence of the associative attributes of memory cells is their responsiveness to task-related stimuli of more than one sensory modality (Haenny et al. 1988; Hikosaka et al. 1988; Maunsell et al. 1991; Colombo and Gross 1994; Gibson and Maunsell 1997; Fuster et al. 2000; Zhou and Fuster 2000, 2004). In the somatosensory
cortex, some cells are attuned to both the touch of an object and the movements of the arm and hand toward it (Nelson and Douglas 1989; Jiang et al. 1991; Lebedev et al. 1994). The same is true in the association cortex of areas 5 and 7 (Hyvärinen and Poranen 1974; Mountcastle et al. 1975; Chapman et al. 1984; Kalaska et al. 1983). From the evidence of associative properties of memory cells, it can be reasonably inferred that these cells belong to wide associative networks. Moreover, the evidence that the cells are activated, in some cases selectively, by the memoranda in WM suggests that this function consists in the activation of cortical memory networks that have been updated and modified for the representation of information toward a prospective goal, that is, a correct and rewarded behavioral act.

The present study further supports the associative and distributed character of parietal networks involved in WM with the following kinds of evidence: 1) single neurons in parietal areas react to the occurrence of several sensory and motor events in the course of a WM task with haptic or visual memoranda; 2) selective memorandum-specific cell activity can be observed during WM in several of those areas (3a, 3b, 1, 2, 5, somatosensory area II [SII], and 7); and 3) in a cross-modal memory task, selectivity of cell response to a haptic memorandum correlates with selectivity of response to an isomorphic visual memorandum.

Materials and Methods
The experiments were conducted on 4 adult male rhesus monkeys weighing between 8 and 12 kg. Two of the animals and their databases were used in previous studies (Zhou and Fuster 1996, 2000, 2004). The animals were individually housed and maintained on a diet of chow and fruit. Fluid intake was restricted before testing sessions. All experiments were carried out under strict adherence to an animal-use protocol periodically reviewed and approved by the University of California, Los Angeles, Chancellor’s Animal Research Committee and in accord with the animal care and experimentation guidelines from the National Institutes of Health (Guide for the Care and Use of Laboratory Animals), the US Department of Agriculture, and the Society for Neuroscience.

Behavioral Paradigms
In a sound-attenuated and electrically isolated chamber, the animals were trained to perform the 2 WM tasks described below, one with tactile memoranda and the other with visual memoranda. Figure 1

![Figure 1](image_url)
depicts the behavioral testing apparatus, the stimuli or memoranda, and the sequence of events in each of the 2 tasks.

**Haptic-Haptic Delayed Match**

Sitting in a primate chair and with its preferred hand on a fixed spherical pedal or handrest, the animal faces an opaque panel with a rectangular opening at the bottom normally occluded by a hinged shutter. A trial begins with a click signaling to the animal the opening of the shutter and the manual accessibility of the sample object: a metallic rod of 19 mm diameter with parallel horizontal or vertical ridges about 6 mm apart. Alternatively, on a variant of the task, the rod has a smooth or rough surface. On hearing the signal, the animal lifts the hand from the pedal and extends it to feel the rod’s surface. After the touch of the sample object, the animal returns the hand to its rest, the shutter closes, and a period of delay follows, during which the animal must memorize the surface of the sample object (the memorandum). The delay lasts somewhere between 10 and 20 s. At the end of that delay, a second click signals again the opening of the shutter and this time the access to 2 rods side by side (11 cm apart from each other), one of them with the surface feature of the sample. The animal palpates one or both objects and chooses one by exerting a slight pull on it. If the chosen object matches the sample, the animal is immediately rewarded with a squirt of fluid. If not (incorrect choice), the trial terminates without reward. A period of about 50 s elapses between one trial and the next. Trials are presented in blocks with the same intratrial delay. The sample and its position at the choice are changed in random order from trial to trial.

**Visual-Haptic Delayed Match**

All 4 animals trained and tested on the Haptic-Haptic (HH) task were also trained and tested on the Visual-Haptic (VH) task. In this task, the sample memorandum is a visual icon: a pattern of parallel horizontal or vertical black stripes (3.5 mm apart) on a white background. The trial begins with the appearance of one such pattern for 3 s on a translucent rectangular screen (about 16 × 10 degrees of visual angle) at eye level in front of the animal (hand remaining in the handrest). The delay ensues, at the end of which a click signals the opening of the shutter and the manual access to 2 rods with parallel ridges—same dimensions and position as in the HH task. The animal must then match and choose the rod with ridges of the same orientation as the stripes of the sample icon.

**Recording**

After training in the HH task (performance criterion 75% correct), the animals were surgically prepared for long-term recording from parietal cortex by implantation of cylindrical pedestrals for support of microelectrode drivers. Before a given recording session, the animal was placed in the testing apparatus with the head fixed and a microelectrode driver on the pedestal above one of the regions of interest. Microelectrodes (0.5–2.0 MΩ impedance) were remotely manipulated into that region during behavioral performance, and their advance halted in the presence of action potential spikes from single units. Electronic switches and sensors registered all the events of a given trial: click, shutter action, contact of the hand with the handrest (if interrupted other than for sample or choice of objects, trial was aborted), choice, and reward. Hand and coarse eye movements were monitored by video cameras. Extracellular spike records were selected for analysis if they were stable, well isolated, and obtained through a sufficient number of correct behavioral response trials. The majority of the records were from areas 1, 2, 3a, 3b, 4, 5a, 7b, and SII (Fig. 2) of the cortex contralateral to the operant hand during performance with the rods. Tactile receptive fields were tested and determined for a number of units, especially in hand areas of somatosensory cortex (1, 2, and 3). After months of daily testing and recording on the HH task, the animals were trained to perform the VH task. Recording during either task took place in successive daily sessions lasting about 3 h on the average. Recorded unit locations were determined by 2 or all 3 of the following methods: presurgical magnetic resonance imaging, stereotaxia, and postmortem histological slide preparations.

**Analysis**

The off-line analysis of the firing frequency of the units recorded during performance consisted of 2 components with 2 corresponding pur-
sample from any region that has been repeatedly penetrated is likely to contain more of the deep units than of the superficial ones.

In all areas, the mean spontaneous intertrial frequency was larger than the median, the difference between the two reflecting the skewness of the frequency distribution. Out of the total database, 896 task-responsive units with stable baseline (no significant average frequency differences between blocks of baseline periods) were selected for further firing-frequency analysis in correct-response trials of either task, HH or VH. Those task-responsive units were defined by: a) statistically significant \((t\text{-}test\; for\; correlated\; means, \; P < 0.05)\) deviations from baseline firing frequency in response to at least 1 of the 6 memoranda during the sample epoch or one of the subsequent delay epochs or b) statistically significant firing difference between the memoranda. Among those units, the baseline firing frequency of cells in primary cortices (areas 1 through 4) was higher than that of cells in nonprimary—"association"—cortex (areas 5, 7, and SI). This difference was highly significant \((P < 0.001)\).

**Unit Firing in HH Delayed Matching**

**Response to Task Events**

The frequency of discharge of each unit was analyzed for differences from baseline firing in relation to the successive event epochs of each HH trial (Table 1): 1) the click that alerted the animal to the accessibility of the sample object, 2) the reach of the arm and hand toward the sample object, 3) the touch of the sample object, 4) the period of delay during which the animal had to retain that object’s features, and 5) the choice of the object that matched the sample. Many cells responded to more than one trial event (Fig. 3). The Venn diagrams in Figure 4 are based on the task-responsive cells that were significantly excited at the sample and/or the delay of the HH tasks (603 units). The diagrams show the percentages of cells within each area or group of areas significantly excited (above baseline) at the click, the reach, and the sample, as well as the delay—the latter jointly with each of those 3 events. Note the considerable overlap of cell responsiveness to the 3 events, as well as between those events and delay activation.

**Response and Selectivity to Haptic Memoranda**

Task-responsive cells in all explored locations of primary and nonprimary cortex (areas 1 through 4, SII, 5a, and 7b)
responded with firing change to the touch of the sample, the majority of them (65.9%) with a significant increase in firing that in many cases persisted during a part or the entirety of the subsequent delay. Usually, the response to the sample was considerably larger than the subsequent delay-period activation. In some cells, the activation at the sample and/or the delay was statistically different depending on the memorandum (Fig. 5).

For the purpose of examining the persistence of memorandum differentiation through the delay period, the units that were significantly excited at the HH sample and/or the delay (603 units) were assessed for correlation between sample Si and delay Si. In all areas investigated—except area 7—the analysis of firing on cell populations pooled by area revealed highly significant (Spearman rank-order test) correlations of memorandum selectivity (Si) between sample and delay periods (Table 2). Such correlations were present in hor-ver trials as well as sm-ro trials; control correlations between sample and baseline periods, as well as between sample and click epochs, were not significant. Also nonsignificant were the sample-delay Si correlations in a group of 48 units from cortex ipsilateral to the operant hand. The significant sample-delay Si correlations indicate that, in large sectors of contralateral cortex, cells maintained memorandum-specific firing during the delay period.

Figure 4. Venn diagrams showing percentage of units in each region activated by or during 3 HH task events (click, reach, and sample). The black histogram bars adjacent to the diagram from each region show the percentage of units (bar outline, 100%) significantly activated during the delay period in addition to the click, the reach, or the sample period.
**Unit-Behavior Correlations**

**Correct versus incorrect performance.** In primary cortices, the Si correlations noted above between sample and delay periods of correct-response trials disappeared, that is, became statistically nonsignificant, in incorrect-response trials. (For this analysis the sample period Si of correct-response trials was compared with delay-period Si of incorrect-response trials; correct-trial sample Si’s were assumed to best represent the normal sample selectivity of each cell.) In area 5, the correlations became negative, that is, incorrect response was on average accompanied by negative Si correlation ($P < 0.05$) between sample and delay—as well as between sample and choice periods.

**Reaction time.** In addition to response correctness, the monkey’s reaction time (RT) was the other measure of performance related in this study to unit discharge. RT was measured between the acoustic signal to choose an object (2nd click) and the lifting of the hand from the handrest for the choice. In one animal, which yielded a relatively large sample of units (353 units from all areas), as well as sufficient records from correct-response trials (7670) and incorrect-response trials (1318), we compared RT with unit discharge frequency in the last 5 s of the delay, that is, in the 5 s just preceding that acoustic signal. In correct-response trials, we found a significant inverse relation between RT and firing frequency ($P < 0.05$). This relationship disappeared in incorrect-response trials. Thus, higher memory-period firing predicted short RT and correct response.

**Unit Firing in VH Delayed Matching**

**Response and Selectivity to Visual Memoranda**

In all areas investigated, cells were seen to change their firing rate at the presentation of the visual sample (icon); in the majority of those cells, as in the HH task, that change was in the form of increased firing (57.0% of task-responsive cells across areas). In a sample of 47 units from SI that were recorded during both tasks, VH and HH, the Si’s of the sample-icon and sample-touch periods were significantly correlated with each other ($P < 0.02$), indicating that the cells differentiated horizontal from vertical orientation similarly whether perceived visually or haptically (Fig. 6). As in the HH task, the analysis of pooled unit activity from primary and nonprimary areas (Table 3) showed that memorandum selectivity (Si) during the delay, as well as during the choice, correlated significantly with selectivity during the sample (in this case, the icon of VH).

**Unit-Behavior Correlations**

**Correct versus incorrect performance.** In a sample of 64 units from primary and nonprimary areas with sufficient number of records from incorrect-response trials, the selectivity maintenance from sample (icon) through delay was assessed as for the HH task (Table 3). In those units, the correlations between sample and delay Si’s, which were significant in correct-response trials, lost their significance in incorrect-response trials. Also in incorrect-response trials, the correlation between sample Si and choice Si became negative ($P < 0.02$).

**Role of learning.** In order to estimate the role of the learning of the VH task on the development of cross-modal and cross-temporal coherence in firing selectivity, long-term unit data from one animal were analyzed as a function of the acquisition of task proficiency through a period of over 1 year. During that period, units were recorded from areas SI, 4, and 5 in a sequence of recording sessions in which the animal performed the VH task—and also the HH task, in which the animal was highly

---

**Figure 5.** Rasters and histograms from a sample- and delay-differential unit through hor- and ver-sample trials. The unit’s receptive field is marked (white) on the hand diagram, the unit’s position (red triangle) on the outlined parietal section on upper left.

---

**Table 2**

Si correlations in HH (ridges) task

<table>
<thead>
<tr>
<th>Area</th>
<th>N</th>
<th>Sample and delay1</th>
<th>Sample and delay2</th>
<th>Sample and delay3</th>
<th>Sample and total delay</th>
<th>Sample and choice</th>
<th>Sample and click</th>
<th>Sample and baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>P value</td>
<td>R</td>
<td>P value</td>
<td>R</td>
<td>P value</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>139</td>
<td>0.47</td>
<td>$P &lt; 0.00001$</td>
<td>0.32</td>
<td>$P &lt; 0.0001$</td>
<td>0.35</td>
<td>$P &lt; 0.01$</td>
<td>0.44</td>
</tr>
<tr>
<td>1,2</td>
<td>151</td>
<td>0.35</td>
<td>$P &lt; 0.00001$</td>
<td>0.31</td>
<td>$P &lt; 0.0001$</td>
<td>0.37</td>
<td>$P &lt; 0.001$</td>
<td>0.34</td>
</tr>
<tr>
<td>5</td>
<td>96</td>
<td>0.46</td>
<td>$P &lt; 0.00001$</td>
<td>0.26</td>
<td>$P &lt; 0.005$</td>
<td>0.14</td>
<td>$P &gt; 0.1$</td>
<td>0.44</td>
</tr>
<tr>
<td>SI</td>
<td>64</td>
<td>0.36</td>
<td>$P &lt; 0.002$</td>
<td>0.29</td>
<td>$P &lt; 0.01$</td>
<td>0.18</td>
<td>$P &gt; 0.05$</td>
<td>0.33</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>0.63</td>
<td>$P &lt; 0.01$</td>
<td>0.34</td>
<td>$P &lt; 0.025$</td>
<td>0.81</td>
<td>$P &lt; 0.01$</td>
<td>0.54</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>0.08</td>
<td>$P &gt; 0.25$</td>
<td>0.16</td>
<td>$P &gt; 0.1$</td>
<td>0.08</td>
<td>$P &gt; 0.25$</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Some units were tested only on trials with 10-s delay; thus, the database for delay3 is smaller than for delay1 and delay2.
proficient throughout. In the course of that sequence of sessions, the animal showed a gradual improvement in the accuracy of VH performance (Fig. 7). As performance of that task improved, significant correlations emerged between visual-sample Si and both delay Si and haptic-choice Si.

Discussion

Response to Multiple Inputs

A salient finding of this study is the responsiveness of cells in multiple areas to multiple events of a behavioral task. In all areas investigated, cells changed their firing rate in temporal relation to several events occurring in the course of the WM tasks: the alerting click, the reach movement toward the sample object, the sample touch or icon visualization, the intratrial (memory period) delay, and the behavioral choice. Whereas some units responded to only one event, the majority responded to more than one. This was true in primary cortex (SI and area 4) as well as nonprimary cortex (SII and areas 5 and 7). In the absence of comprehensive unit data acquired during the learning of the tasks, it is difficult to ascertain that the multiple-event cellular responsiveness developed with the establishment of neural associations between the tasks’ events and, therefore, reflected the cells’ involvement in those associations. Such an interpretation appears plausible, however, by considering that the events eliciting cellular responsiveness are operationally indispensable for correct performance of the task. In any case, the participation of the reported cells in the neural network that represents the basic tasks with all their associated components is supported by a) the relationships between unit activity and behavioral measures (level of performance and RT), b) the anatomical proximity of cells responding to different events within any of the areas explored, and c) the cellular acquisition of sample-delay selectivity in the process of learning the VH task.

The anatomical access of the auditory input (click) to the cortical network that represents and coordinates the haptic task is unclear. There are at least 2 possible lines of access: 1) connections from auditory areas through the claustrum, which is implicated in cross-modal associations (Ettlinger and Wilson 1990; Hadjikhani and Ronald 1998) and 2) connections from posterior association areas (Pandya and Yeterian 1985). As we have argued in a previous study (Zhou and Fuster 2004), by virtue of its associations with the network that represents the task, the auditory input from the alerting click starting the HH trial may act as the “igniter” (Braitenberg 1978) which makes that network operational for the trial. After the click, the cells involved in the hand reach toward the haptic sample are presumably the next associative and operant link of the activated network. This movement is accompanied by the presence of reach-activated cells in motor as well as sensory areas. The activation of those cells most likely reflects the processing of the movement as well as the arrival of proprioceptive inputs that the movement elicits in the periphery (Tanji and Wise 1981; Nelson 1988; Burbaud et al. 1991; Germain and Lamarre 1993).

One of our surprising findings was the pervasiveness of cells that were activated during sample touch, not only in primary motor and somatosensory cortices but also in associative areas (5 and 7). The activations of cells in SI could be easily attributed to thalamic inputs of somesthetic or proprioceptive origin. Yet, those cells too exhibited associative properties, in that they also responded to auditory and visual inputs from the tasks. Those inputs probably reached the cells from posterior association cortex (Jones and Wise 1977; Friedman 1983; Pandya and Yeterian 1985; Taylor-Clarke et al. 2002). The sample-responsive cells in associative areas, however, may have been activated not only by tactile but also by nontactile sensory inputs related to the sample, such as its position in space. These inputs may also be a part of the same representational and operational network of the task that is activated (rather, reactivated) by the sample object.

The finding of cross-modal neuronal transfer of information about orientation from vision to touch through WM—in the VH

![Figure 6](image-url). Rasters and histograms from a delay-differential unit recorded during the VH task. Rasters are graphed for the 10-s period prior to the choice.

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>Sample and delay1</th>
<th>Sample and delay2</th>
<th>Sample and delay3*</th>
<th>Sample and total delay</th>
<th>Sample and choice</th>
<th>Sample and baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>R</td>
<td>P value</td>
<td>N</td>
<td>R</td>
<td>P value</td>
</tr>
<tr>
<td>Correct</td>
<td>90</td>
<td>0.33</td>
<td>P &lt; 0.001</td>
<td>0.41</td>
<td>P &lt; 0.0005</td>
<td>0.55</td>
</tr>
<tr>
<td>Incorrect</td>
<td>64</td>
<td>0.00</td>
<td>P &gt; 0.9</td>
<td>0.05</td>
<td>P &gt; 0.6</td>
<td>−0.10</td>
</tr>
</tbody>
</table>

*Some units were tested only on trials with 10-s delay; thus, the database for delay 3 is smaller than for delay 1 and delay 2.
task—is similar to that of a comparable transfer reported by Maunsell et al. (1991) in area V4. If our interpretation of Si coherence in parietal firing during the VH task is correct, cells in visual cortex are also likely a part of the memory network which represents that task and mediates its performance. At higher levels, in the lateral prefrontal cortex, cross-modal association has also been observed (Fuster et al. 2000). As in parietal cells of this study, cells in prefrontal cortex respond in correlated manner to stimuli of different modality: tones and colors that have been paired in a cross-modal WM task (Fig. 8). Further, the cross-modal association between tones and colors is maintained across the delay or memory period (Fig. 9); the cells associate colors with tones in WM in accord with the rules of the task that the animals have learned to perform through months of training prior to recording. It is reasonable to conclude that the responsiveness of those cells to tones and colors, across time (delay) and across modalities, like the VH transfer in the experiments described above, is the result of the acquisition of those cross-modal associations in the establishment of the task in long-term memory by virtue of the learning process. Also, inasmuch as they are activated by or during other task events, delay-activated neurons belong to the hypothetical long-term memory network that represents the tasks. One of us (Fuster 1999, 2003), based on the review of data from several methodologies (i.e., neuropsychology, neurophysiology, and neuroimaging), has argued for the commonality of neural substrate for long-term memory and WM. With regard to the cortical dynamics of that substrate, the seriatim involvement of cortical neurons in successive task events, as our data indicate, leads to the reasonable inference that the performance of a task depends on the orderly activation of the neural components of the large memory network that constitutes that substrate.

**Discrimination and WM**

Cells that in the HH task responded to the sample objects were likely involved in the perception and discrimination of those objects by surface feature or memorandum (hor vs. ver, sm vs. ro). A substantial portion of the firing increase elicited in those cells by the sample touch was clearly not differential (not related to surface feature) and thus related to aspects of the object samples other than their surface feature. To the degree that the cells differentiated surface features, they discriminated the somesthetic or proprioceptive inputs that the haptic touch of the memoranda elicited. Also to the degree that the cells discriminated the memoranda, it can be inferred that they participated in their encoding in WM. The presence of differential—that is feature dependent—firing during the subsequent delay denoted the cells’ participation in the mnemonic retention of the memorandum in parietal as well as in prefrontal cortex. Indeed, the correlations of Si between sample and delay periods implicate large numbers of parietal cells in the WM of surface tactile features. Remarkably, cells with significant sample-delay Si correlations were found in both the primary (including motor cortex) and nonprimary areas examined (at the exception of
evidence that prefrontal cells are involved in parametric WM of both HH and VH tasks (Shindy et al. 1994); the second is the prefrontal cryogenic inactivation induces reversible deficits on support of this assumption. The first is the evidence that Pandya 2002). There are 2 lines of direct experimental evidence prefrontal cortices (Jones and Powell 1969, 1970; Petrides and 2000; Brunel and Wang 2001; Laing and Chow 2001).

Figure 9. WM discharge attuned to a sound/color association in long-term memory (the task rule). Average frequency histograms of 3 cells which, in the task of Figure 8, prefer the low tone. During the delay, their discharge is higher between low-tone sample and green choice than between high-tone sample and red choice. At the choice of color, the 2 lower cells show clear preference for green, the color matching low tone (Fuster et al. 2000).

Despite a reported high degree of delay-activity variance at the level of the single cell (Shafi et al. 2007), at the population level the present haptic study shows widespread delay differentiation coherent with sample differentiation in most of the areas examined. This further points to a widely distributed, stochastically highly robust WM code. Moreover, a study of patterns of cell discharge during the delay of the HH task (Bodner et al. 2005) shows certain periodicities of discharge indicative of network reentry, which may not only apply to local but also to corticocortical circuitry. Thus, haptic WM is conceivably maintained by recurrent or reverberating activity within a broad cortical network. This is congruent with computational models of WM in which reentry is an essential feature of the structural and functional architecture of WM (Tononi et al. 1992; Zipser et al. 1993; Amit and Brunel 1997; Compé et al. 2000; Brunel and Wang 2001; Laing and Chow 2001).

**Perception-Action Cycle**

The haptic WM network, as any other WM network of posterior cortex, probably extends into prefrontal areas by way of the well-established anatomical connections between posterior and prefrontal cortices (Jones and Powell 1969, 1970; Petrides and Pandya 2002). There are 2 lines of direct experimental evidence in support of this assumption. The first is the evidence that prefrontal cryogenic inactivation induces reversible deficits on both HH and VH tasks (Shindy et al. 1994); the second is the evidence that prefrontal cells are involved in parametric WM of tactile stimuli, that is, vibrations of different frequencies delivered to the surface of the hand (Romo et al. 1999). Then there is the extensive evidence of involvement of prefrontal units in the WM retention of a large variety of sensory memoranda (see Fuster 2001 for review). In visuomotor WM (where the memorandum is a position in visual space and the animal, after a delay, must make an eye saccade to it), some aggregates of prefrontal cells are so sharply tuned to the memorandum as to suggest specialized memory modules or maps in dorsolateral prefrontal cortex (Funahashi et al. 1989; Goldman-Rakic 1995). Nonetheless, such modules or maps may, themselves, be constituents of larger networks (Goldman-Rakic 1988).

All that evidence points to the prefrontal cortex as the integrator of sensory information for its maintenance in WM, and therefore a participant in WM, but not necessarily the seat of WM. The seat of WM, instead, is likely to be the entire network or a large sector of it, with its sensory components in posterior cortex and its motor components in frontal cortex. When the network is activated at the beginning of a WM trial and all its associated components transit from representation to operation, the prefrontal components become “executive,” which means, they guide the processing in the entire network toward the behavioral goal. This prefrontal guidance or “executive control” (Desimone and Duncan 1995; Fuster 1997; Miller 2000) is probably nothing other than the orderly activation of that cortical network and subcortical nuclei in the adaptive pursuit of the goal. The processing of that order in the cortical network, however, is not only serial and feed-forward, but also largely parallel and with abundant feedback.

Feedback reentry is essential to any biological system. In the structuring of sequential goal-directed behavior, there are at least 2 forms of reentry likely to assist prefrontal executive control. One is the continuous flow of sensory information about the changes that successive actions produce in the environment, changes that in turn inform further action. The other is the recurrent and reciprocal reentry that maintains active the cortical network dynamically linking sensory inputs with executive outputs until the goal is attained. Both forms of reentry are part of the perception-action cycle (Fuster 2001), as illustrated in Figure 10. If the sequence contains temporal discontinuities and requires the mediation of cross-temporal contingencies, as delay tasks do, then the second type of reentry probably becomes critical to the maintenance of WM in the network at the top of the perception-action cycle. This kind of reentry presumably consists of reverberation between posterior and prefrontal network circuits. Interruption of the cycle at the top, by cooling frontal or posterior areas, leads to failure of both WM and delay activity (Fuster et al. 1985; Quintana et al. 1989; Chafee and Goldman-Rakic 2000).

In a large-scale cortical network embedded in the perception-action cycle, with its reciprocal connectivity and reentry between posterior and frontal areas, it is practically impossible to separate the cortical substrate of perception from that of action. The dynamic circularity and reentry within the system preclude a true cortical origin for either perception or action. Thus, during goal-directed behavior, cells in both perceptual and executive cortices may appear to engage in both, perception and action. Depending on the experimental context, some cells may appear more committed to perception than to action, others the reverse. This may be the reason for the paradoxical finding of neurons with apparent executive functions (“command” and “decision making”) in parietal cortex or neurons
with "sensory" properties in prefrontal cortex. Perhaps the so-called "mirror neurons" (Rizzolatti et al. 1990) epitomize the difficulty to disambiguate the representation of the percept from that of the action it represents. At the same time, these same neurons seem to affirm an old, often forgotten, principle first enunciated by Jackson (1882) based on his extensive experience with cortical injuries. The same areas that represent a movement are in charge of its coordination. He postulated that the same principle applied to higher frontal cortex and the presumably more complex actions it coordinates.

The interpretation of our results elevates the identity of representational and coordinating substrates for WM from the level of a cortical area (parietal or prefrontal) to the level of the large-scale cortical network. As these results indicate, the associative aspects of a haptic WM task are distributed in a wide network of neurons in motor and parietal areas. This network probably extends to basal ganglia and other subcortical formations that contribute the "procedural" or habit-driven aspects of the task. It probably extends also to the prefrontal cortex, where the goal-directing aspects of the task are represented and coordinated. One of those aspects is the bridging of time, the mediation of cross-temporal contingencies within the task—and within the network—at the top of the perception-action cycle. This mediation is a role of WM, the timely and sustained activation of those elements of the long-term memory network that, within the broad associative representation of the task, represent the memorandum of every trial with all its associated features. Ultimately, the cortical dynamics of WM will be conclusively elucidated by the integrated use of multiple methodologies in multiple areas and at different levels of resolution.

**Funding**

National Science Foundation (IBN-9308905); the Whitehall Foundation (597-13); the National Institute of Mental Health (MH-25082 and MH-51697).

**Notes**

We gratefully acknowledge the technical assistance from William Bergerson (hardware) and Bradford Lubell (software). We are also indebted to JoMarie Tran Janco, Sung-Hee Park, and Monika Siman for their help in the conduct of the experiments, as well as Ivo Dinov for statistical advice. Yixuan Ku provided valuable help in the analysis of the data. Conflict of Interest: None declared.

Address correspondence to Joaquin M. Fuster, Semel Institute for Neuroscience, University of California, Los Angeles, 750 Westwood Plaza, Los Angeles, CA 90095, USA. Email: joaquinf@ucla.edu.

**References**


