

A Neural Circuit Basis for Spatial Working Memory

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The maintenance of a mental image in memory over a time scale of seconds is mediated by the persistent discharges of neurons in a distributed brain network. The representation of the spatial location of a remembered visual stimulus has been studied most extensively and provides the best-understood model of how mnemonic information is encoded in the brain. Neural correlates of spatial working memory are manifested in multiple brain areas, including the prefrontal and parietal association cortices. Spatial working memory ability is severely compromised in schizophrenia, a condition that has been linked to prefrontal cortical malfunction. Recent computational modeling work, in interplay with physiological studies of behaving monkeys, has begun to identify microcircuit properties and neural dynamics that are sufficient to generate memory-related persistent activity in a recurrent network of excitatory and inhibitory neurons during spatial working memory. This review summarizes recent results and discusses issues of current debate. It is argued that understanding collective neural dynamics in a recurrent microcircuit provides a key step in bridging the gap between network memory function and its underlying cellular mechanisms. Progress in this direction will shed fundamental insights into the neural basis of spatial working memory impairment associated with mental disorders. *NEUROSCIENTIST* 10(6):553–565, 2004. DOI: 10.1177/1073858404268742

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The ability to hold information in memory over a time scale of seconds is a critical component of cognitive functions such as language, abstract thought, planning and most of the mental processes we associate with human intelligence. Working memory, as this critical function is known, can be thought of as a blackboard of the mind (Baddeley 1992). Because of its central role in cognitive function, working memory has attracted intense research scrutiny over several decades. Early, lesion studies revealed profound short-term memory deficits after selective ablation of the prefrontal cortex (Jacobsen 1936; Milner 1963; Goldman-Rakic 1987). Subsequent neurophysiological experiments in monkeys demonstrated that prefrontal neurons continue to discharge even after the offset of transient sensory stimuli that animals are required to remember (Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi and others 1989). This persistent discharge is widely thought to be the neural correlate of working memory. The

advent of imaging techniques, PET and fMRI, verified persistent activation of the human brain during the maintenance of information in memory and confirmed the involvement of the prefrontal cortex in the process (Jonides and others 1993; Courtney and others 1997; Ungerleider and others 1998). Neural correlates of working memory have since been observed in other brain regions as well, and indeed, the prefrontal cortex is only part of a broader network of interconnected cortical and subcortical areas (Fig. 1). The differential roles and relative contributions of these brain structures in memory function continue to be investigated.

The representation of spatial information and particularly the position of a visual stimulus on the fronto-parallel plane has been a popular model for the investigation of working memory. Among its advantages is that space is represented in the brain in a well-understood, parametric fashion; the primary visual cortex is organized retinotopically, providing a clear correspondence between neuronal activity and stimulus position. In contrast to retinal location, the representation of other stimulus attributes (e.g., object identity) is encoded in still poorly understood dimensions. Visuospatial memory tasks (Fig. 1) provide the best-understood model of working memory, and much effort has been devoted to understanding the cortical mechanisms underlying their execution. This review summarizes recent progress in the field, with an emphasis on close interactions between experimental and computational approaches that have

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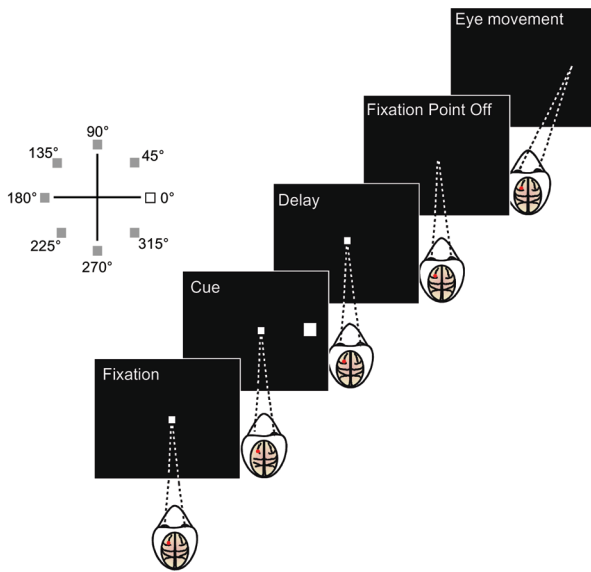


Fig. 1. Successive frames illustrate the sequence of events in the oculomotor delayed-response task. Trials begin with the appearance of a fixation point at the center of the screen, which the monkey is required to foveate throughout the trial. A spatial cue is subsequently presented, typically at one of eight locations (*left*). After a delay period of a few seconds, the fixation point is turned off and the monkey is required to indicate the location of the cue by moving his eyes accordingly on the screen.

led to new insights, as well as open questions for future investigations.

Neural Correlates of Spatial Working Memory

Electrophysiological studies in the monkey prefrontal cortex (Fig. 2) first revealed that a population of prefrontal neurons continues to discharge in a persistent fashion, even after sensory stimuli are no longer present (Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi and others 1989). The part of the visual space where stimulus appearance can produce sustained activation has been termed the neuron's *memory field*, in analogy to the receptive field of neurons responding to sensory stimulation. Different prefrontal neurons exhibit different memory fields, and the overall activity of the population can encode the location of a remembered stimulus.

To elucidate the neural mechanisms of spatial working memory, it is desirable to dissect neural activity related to the mnemonic content per se, dissociated from the other aspects of a behavioral task. One of the most often-used, as well as simplest, behavioral paradigms for evaluating persistent activity is the oculomotor delayed-response task (Fig. 2). In this task, monkeys are required to fixate a central point on a screen, to remember where a brief visual cue appeared, and after a delay period of a few seconds, to indicate the remembered location of the cue by shifting their eyes to it. Neuronal activity persisting after the disappearance of the visual cue in such a task may, in principle, mediate the memory of the cue

location but may also be related solely to the preparation of the motor response. Indeed, one of the disadvantages of the visuospatial model is that spatial information in the brain is inexorably linked with motor circuits for the guidance of eye and limb movements to visual targets. It is a challenge, therefore, to dissociate experimentally observed neuronal activity related to visual spatial memory with that related to the preparation of motor commands. A number of experiments have sought to distinguish between the two alternatives by dissociating the location of a remembered stimulus with the direction of a motor response. Monkeys have been trained to perform an antisaccade task requiring an eye movement away from a remembered stimulus (Funahashi, Chafee, and others 1993), a conditional response task involving a movement in a direction other than the stimulus location (Niki and Watanabe 1976; Takeda and Funahashi 2002), or a spatial match to sample task, demanding a lever release when a stimulus appears at a previously cued location (Sawaguchi and Yamane 1999). In all cases, discharge of the majority of dorsolateral prefrontal neurons was found to encode the location of the remembered stimulus, although a minority of neurons did represent the actual motor response. A signal-detection theory analysis of prefrontal cortical activity revealed that the latter reflects sensory attributes of a remembered stimulus even when the particular stimulus is not guiding a motor action (Constantinidis and others 2001b).

Although visual stimuli have been most extensively used in neurophysiological investigation, spatially localized mnemonic neuronal activity is not restricted to vision. Prefrontal cortical neurons exhibit sustained discharges in auditory memory tasks, spatially tuned to the location of the sound source (Azuma and Suzuki 1984; Vaadia and others 1986; Bodner and others 1996). A particular prefrontal cortical subdivision appears to receive specialized inputs of spatial auditory information (Romanski and others 1999). Beyond the prefrontal cortex, neurons in lateral intraparietal area (LIP) of the posterior parietal cortex have been shown to be active during tasks requiring orienting to a remembered auditory target (Mazzoni and others 1996) but only if they have been trained to perform an eye-orienting task to auditory stimuli (Grunewald and others 1999).

Working Memory in a Distributed Network

Although first described in the prefrontal cortex, neurons active during spatial working memory have been reported in other cortical areas. The dorsolateral prefrontal cortex (areas 46 and 8) receives input from the posterior parietal cortex, an area of the dorsal visual stream, which is involved with the processing of visuospatial information. Posterior parietal neurons in areas LIP and 7a (Fig. 3) are tuned to the spatial location of stimuli, and they too discharge in a sustained fashion when animals are trained to remember the spatial location of a stimulus (Andersen and others 1987; Gnadt and Andersen 1988; Quintana and Fuster 1992; Constantinidis and Steinmetz 1996). A study comparing

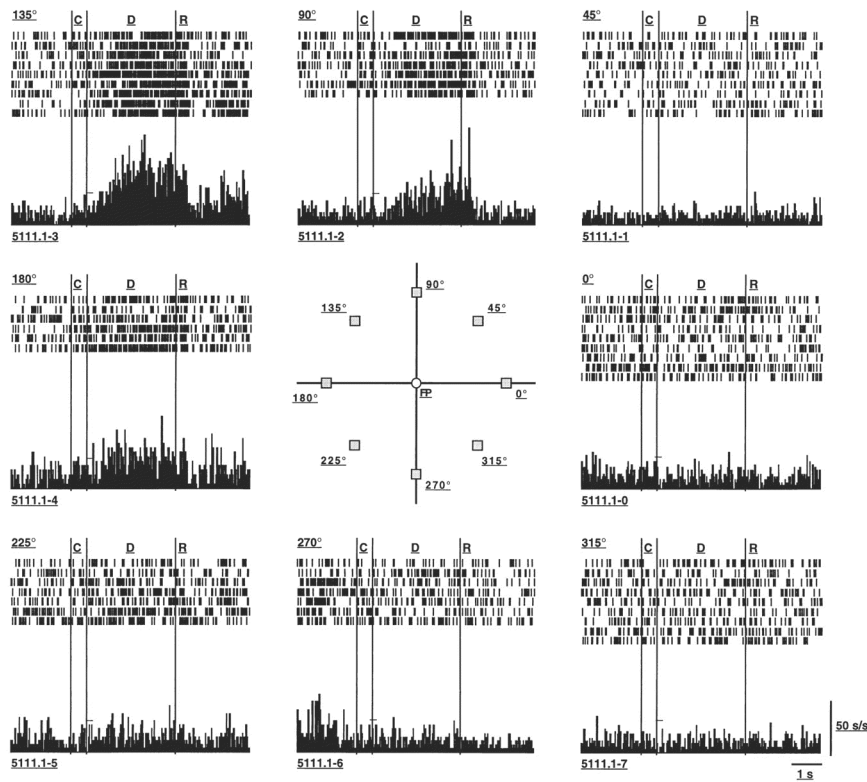


Fig. 2. Activity of a single prefrontal neuron, exemplifying persistent discharges during the execution of the oculomotor delayed-response task. Discharges are arranged as to indicate the location of the cue. The neuron is mostly active during the delay period following presentation of a stimulus in the upper left (135-degree) location. From Funahashi and others (1989) with permission.

responses in the dorsolateral prefrontal and posterior parietal cortex of the same monkeys trained to perform an oculomotor delayed-response task revealed no appreciable differences in the two areas (Chafee and Goldman-Rakic 1998). Indeed, imaging studies in humans almost invariably report concurrent prefrontal and parietal activation in working memory tasks (Jonides and others 1993; Courtney and others 1997; Owen and others 1998; Ungerleider and others 1998; Marshuetz and others 2000; Bunge and others 2001; Rowe and Passingham 2001; Stern and others 2001; Munk and others 2002). The distinct and cooperative roles of these areas remain unresolved.

Memory-related activity has been further described in earlier areas of the dorsal visual pathway projecting to the posterior parietal cortex, such as area V3A and MT (Nakamura and Colby 2000; Bisley and others 2004) and even V1 (Super and others 2001). In addition, spatial memory responses have been recorded in the primate entorhinal cortex (Suzuki and others 1997). Also active during spatial working memory are brain areas involved in the control of movement, such as the premotor and supplementary motor cortex (di Pellegrino and Wise 1993b; Russo and Bruce 1996), superior colliculus (Glimcher and Sparks 1992), and basal ganglia (Hikosaka and Wurtz, 1983; Hikosaka and others 1989; Kimura and others 1992). These results show that

mnemonic neural activity is widespread. However, information is scarce as to whether persistent activity is primarily generated in certain local brain areas, while neurons in other areas simply reflect sustained inputs from memory cells upstream, or persistent activity depends on feedback connection pathways in a large brain network. There have been conflicting reports on whether delay-period-persistent activity is prevalent in the thalamus (Fuster and Alexander 1973; Sommer and Wurtz 2004). The clarification of this issue would help to assess whether the cortico-thalamic-basal ganglia loop is critical to the generation of working memory activity in the cortex.

Important differences between the activation of the prefrontal and posterior parietal cortex have begun to be unveiled through the use of more complex cognitive tasks. When monkeys are trained to remember the spatial location of a sample stimulus and ignore intervening, distracting stimuli, neurons in posterior parietal areas 7a and LIP encode the location of the most recent stimulus, whether it is the remembered sample or the behaviorally irrelevant distractor. Parietal neurons respond in a persistent fashion to the presentation of distractor stimuli in the receptive field (Constantinidis and Steinmetz 1996; Powell and Goldberg 2000) while ceasing to represent the sample stimulus, although the animal continues to retain the sample in memory and successfully completes

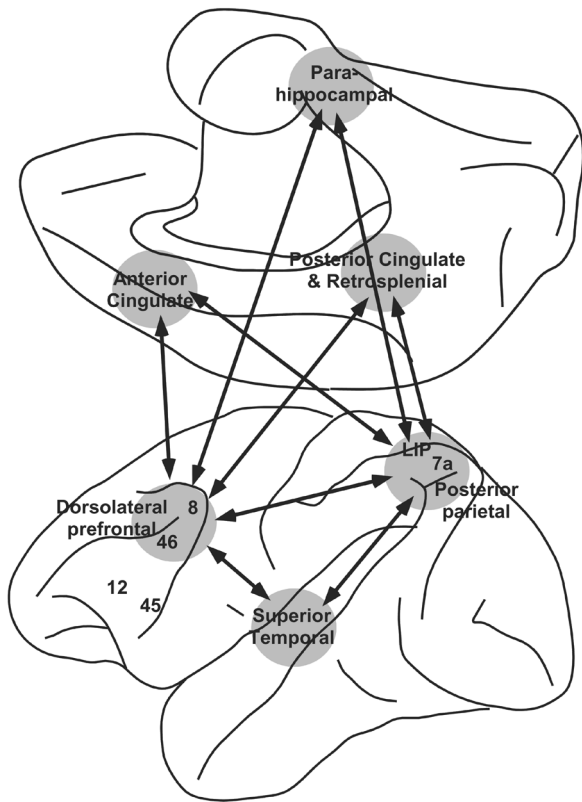


Fig. 3. The spatial working memory network. Cortical areas anatomically interconnected with the dorsolateral prefrontal cortex and activated by spatial memory.

the trial. Prefrontal neurons, on the other hand, encode the actively remembered cue (di Pellegrino and Wise 1993a, 1993b). This prefrontal trait of resistance to sequentially presented distractors has been recently verified by human imaging experiments (Cornette and others 2002; Sakai and others 2002). Computational studies have offered insights on how a working memory network can filter out behavioral irrelevant stimuli, suggesting a possible role of NMDA receptors, dopamine innervation, and specialized interneuron types (Compte and others 2000; Brunel and Wang 2001; Wang and others 2004).

Responses of neurons activated by spatial working memory can be modulated by other factors, as it has recently been revealed by the use of more complex behavioral paradigms. When the animal is cued to remember one of multiple stimuli in the visual field, prefrontal neurons preferentially represent the attributes of the attended stimulus (Rainer and others 1998b; Everling and others 2002). The response of prefrontal neurons to the same operant stimuli can also vary depending on the expectation of reward, when the later changes from trial to trial (Leon and Shadlen 1999). A similar modulation of neuronal responses to identical stimulation has been observed in animals trained to perform a number of alternative tasks, requiring association of the same stimulus with different possible motor

choices, according to different rules (White and Wise 1999; Asaad and others 2000; Wallis and others 2001). Prefrontal activation by such nonspatial factors has been readily observed in human fMRI experiments, leading some experimenters to question whether the role of prefrontal cortical activity is spatial in nature at all (Curtis and D'Esposito 2003). Such a view is difficult to reconcile, however, with the unequivocal spatial tuning of neuronal activity recorded in neurophysiological experiments. Effects of cognitive functions such as attention and reward expectation have been demonstrated in other areas of the working memory network, most extensively in the posterior parietal cortex (Platt and Glimcher 1999; Constantinidis and Steinmetz 2001). How spatial location can be decoded independently of other factors modulating neuronal activity is still an open question.

Microcircuit Organization of Spatial Working Memory

There has been some debate about whether the ventral subdivision of the prefrontal cortex comprising areas 12 and 45 (the prefrontal inferior convexity) might have a role in spatial memory as well. These areas receive input from the inferior temporal cortex, the final stage of the ventral visual pathway, and for this reason have been thought to represent memory for the identity of stimuli (Wilson and others 1993). However, it has been suggested that inferior convexity neurons might represent spatial information as well, and conversely dorsolateral prefrontal neurons might represent stimulus identity, particularly after animals have been trained to perform a memory task that requires them to remember both the location and identity of a stimulus (Rao and others 1997; Rainer and others 1998a). These experiments led to the suggestion that information for spatial location and identity might be combined in the prefrontal cortex. Newer studies shed light on this apparent discrepancy. It has now been demonstrated that the object selectivity observed in dorsolateral prefrontal neurons could be accounted for by broad but significant tuning to stimulus shape already present at the level of the posterior parietal cortex (Serenio and Maunsell 1998). Similarly, neurons in the inferior temporal cortex can be highly selective for spatial position (DiCarlo and Maunsell 2003). The selectivity for object and spatial information is therefore a matter of degree (a gradient) in the prefrontal cortex, as a result of the cross-talk between the dorsal and ventral visual pathways upstream and possibly through reciprocal connections between the dorsal and ventral subregions of the prefrontal cortex. In addition, experience-dependent plasticity might endow prefrontal cortical neurons with the ability to encode combined object and spatial information, which could be used to subserve flexible sensorimotor association in behavioral control (Asaad and others 1998; White and Wise 1999).

Within a prefrontal subregion (say, area 46), previous experiments have failed to establish a clear pattern of topographic organization of prefrontal (or posterior pari-

etal) memory fields, unlike the primary visual cortex, in which the entire visual space is represented topographically across the cortical surface. Despite the apparent lack of an overall retinotopic map across the surface of the prefrontal cortex, there is strong evidence for a systematic organization of spatial information at a local level. Localized prefrontal lesions produce behavioral deficits in the execution of mnemonic tasks involving only a restricted area of visual space, typically in the contralateral hemisphere, an effect known as a “mnemonic scotoma” (Funahashi, Bruce, and others 1993). Similarly, chemical inactivation of prefrontal sites produces the inability of monkeys to correctly recall targets appearing at certain spatial locations (Sawaguchi and Goldman-Rakic 1991, 1994), which again is an argument for an organized representation of visual space in the cortex. More recently, simultaneous recordings from closely spaced electrodes have confirmed that neurons in the proximity of each other (laterally separated by less than 0.3 mm) most often represent adjacent spatial locations (Constantinidis and others 2001a). A possible organizational scheme that could account for these results would be for the entire visual hemifield to be represented in repeating, topographically organized cortical modules, perhaps corresponding to the anatomical stripe-like zones of axonal terminations (Levitt and others 1993; Kritzer and Goldman-Rakic 1995; Pucak and others 1996).

Cellular Mechanisms of Spatial Working Memory

The maintenance of neuronal discharge representing remembered information can last for several seconds, much longer than the time constants of single-neuron biophysical processes, and it is therefore thought to be foremost a network function. Single neurons may also be bistable due to intrinsic membrane properties that contribute to network behavior (Camperi and Wang 1998; Wang 2001). Indeed, a recent study of *in vitro* slice recordings reports that individual neurons in the entorhinal cortex are capable of producing graded persistent discharges (Egorov and others 2002). How a network can give rise to sustained activation in the absence of a direct sensory stimulation can be illustrated as follows: A visual stimulus produces activation of primary visual cortical areas, which is ultimately propagated to the prefrontal cortex, where it excites a population of pyramidal neurons tuned to its location in space. These neurons are linked through reciprocal, excitatory synaptic connections so that even when the original stimulus is no longer present, discharges continue to reverberate in the network (Wang 2001). The anatomical organization of the prefrontal cortex in many ways resembles a recurrent neural network (Fig. 4). Axonal projections of pyramidal neurons originating from within the prefrontal cortex (intrinsic projections) as well as from other cortical areas (associational projections) terminate in a precise stripe-like fashion, creating a regular pattern of interdigitated columns, approximately 0.5 mm wide and 2 to 8 mm

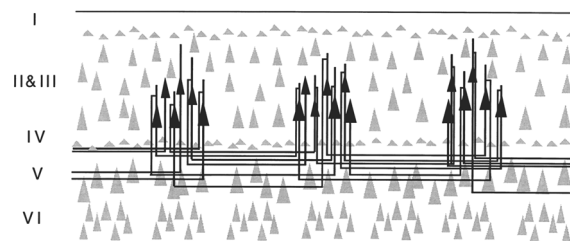


Fig. 4. Schematic diagram illustrating the pattern of connections between prefrontal neurons in the superficial layers. The figure summarizes results of anatomical tracer injection experiments and retrograde labeling. From Kritzer and Goldman-Rakic (1995), with permission.

long (Levitt and others 1993; Kritzer and Goldman-Rakic 1995; Pucak and others 1996). Reciprocal connections between neurons in such stripes create the anatomical substrate of a recurrent network.

Biophysically realistic computational modeling has shown that such recurrent networks can give rise to location-specific, persistent discharges, as illustrated in Figure 5 (Camperi and Wang 1998; Compte and others 2000; Gutkin and others 2001; Tegner and others 2002; Renart and others 2003a, Wang, Tegner, and others 2004). The central conceptual idea that emerges from these studies is that a spatial working memory network should be bistable between a spontaneous resting state and a continuous family of spatially localized persistent firing patterns (each encoding and storing a spatial location as an analog quantity). The appearance of the transient cue stimulus switches the network from the resting state to a memory state representing a spatial location, and the feedback signal or reward that indicates the end of the trial erases the memory trace and switches the network back to its resting state. It was realized that the instantiation of a continuum of persistent states requires the cortical network to be functionally homogeneous, that is, to be characterized by identical cellular and synaptic properties between its neurons. Such homogeneity is unrealistic for real-neuron networks but could be effectively achieved by biological mechanisms such as homeostatic regulations that could scale the synaptic inputs of neurons with different rates of activity (Renart and others 2003a). It is also worth noting that the continuous nature of spatial working memory has not been scrutinized in experimental studies, in which only a limited number (typically eight) of spatial cues are used. It would be desirable in future psychophysical and electrophysiological studies to rigorously test the analog character of spatial working memory by using an arbitrary set of cues.

Understanding the dynamical behavior of strongly recurrent cortical microcircuits, including those presumably required for persistent activity, presents experimental and theoretical challenges. In biophysically realistic models, such a neural network is prone to dynamical destabilization leading to either uncontrolled spike discharges at very high rates, if excitatory reverberation is

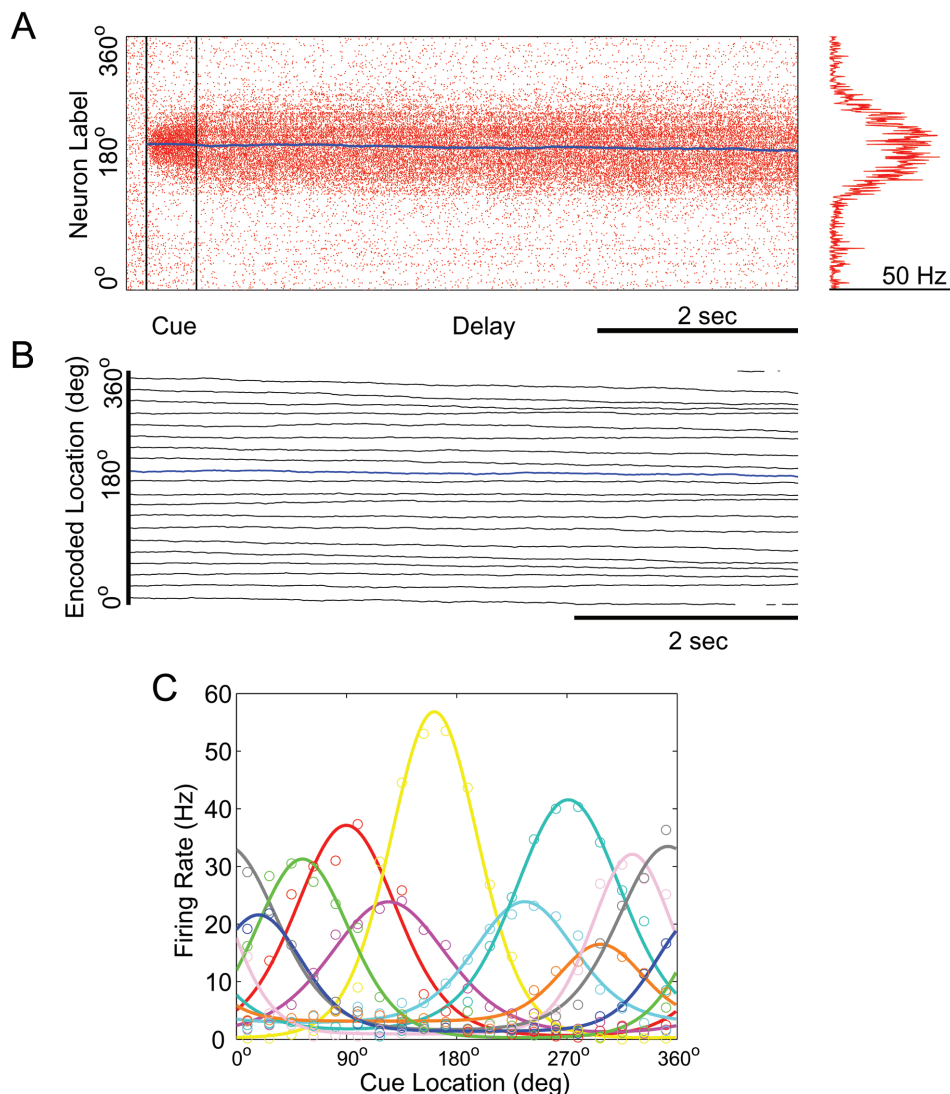


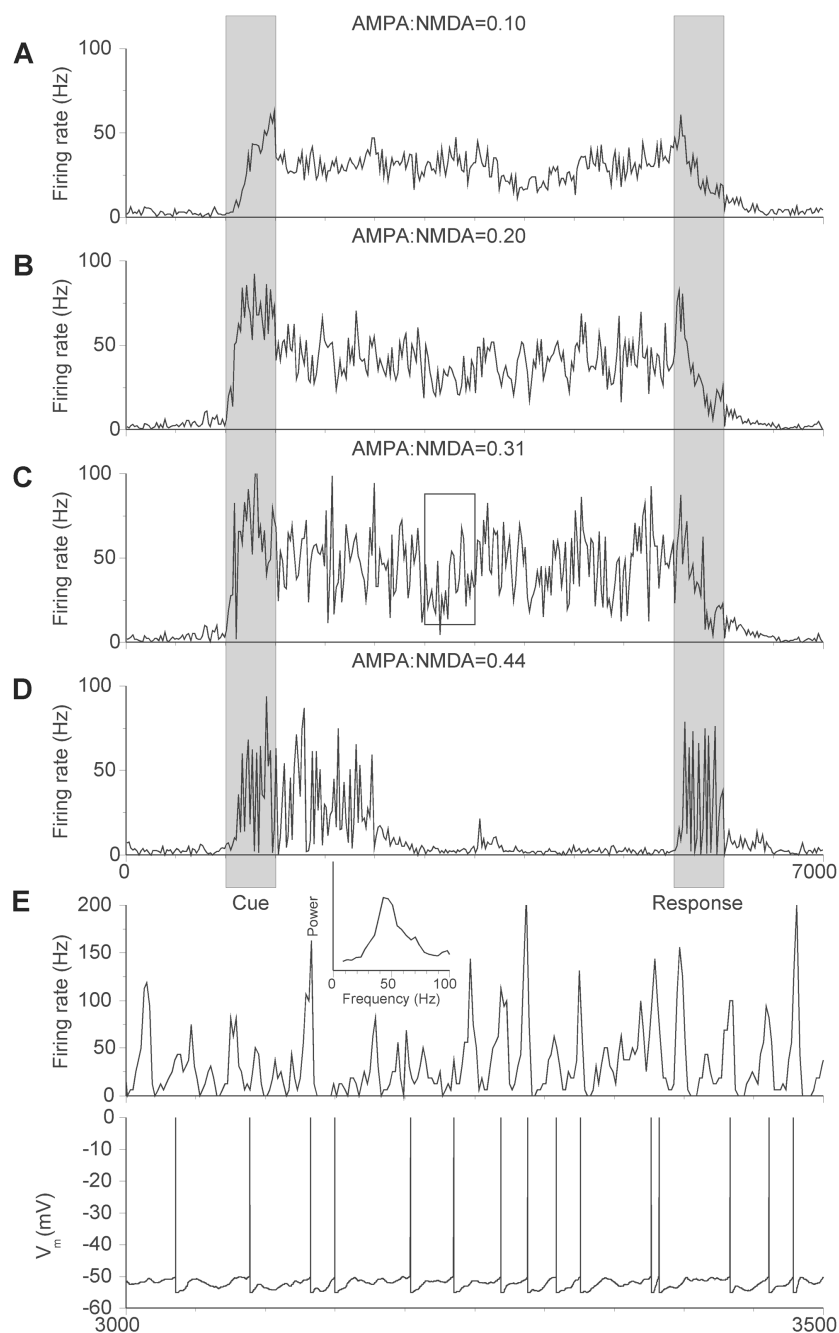
Fig. 5. A, Model simulation of the delayed oculomotor response experiment (Figs. 1, 2). Spatiotemporal activity pattern of the pyramidal cell population. A dot at position (t, θ) represents a spike fired at time t by a cell with preferred cue location at direction θ . The blue line represents the time evolution of the peak location of the persistent activity pattern. Right, localized activity profile during the mnemonic delay period. B, Temporal evolution of the peak location of memory activity in 20 trials with transient stimuli at different locations. The memory of the initial cue is well preserved during the 6-second delay period. C, Tuning curves from 10 neurons. The firing rate of each cell for the 20 stimuli in (B) is shown as open circles. Adapted with permission from Renart, Song, and others (2003).

not counterbalanced by rate-control mechanisms, or to excessive synchronous oscillations that may be disruptive to the maintenance of persistent activity. Working memory function was found to be particularly stable (Fig. 6) when excitatory reverberation was characterized by a fairly slow time course, for example, when synaptic transmission at intrinsic connections incorporated a large NMDA component (Wang 1999; Compte and others 2000; Wang 2001; Tegner 2002; Renart and others 2003b). NMDA receptor-mediated recurrent excitation may also be especially important for the robustness of short-term memory that encodes continuous quantities, such as spatial location or eye position (Seung and others 2000). The voltage dependence of NMDA channels may contribute to stimulus selectivity of a persistent firing pattern (Lisman and others 1998).

Temporal Dynamics of Persistent Activity

An interesting question is whether working memory is stored mainly in the elevated firing rate of a subpopulation of neurons or depends on more complicated temporal discharge patterns and cross-neuronal synchrony. In principle, stimulus information can be conveyed by different temporal patterns of activity without any variations in the average firing rate of a neuron. In fact, under some conditions, the averaged responses of the entire prefrontal population may vary little between a spontaneous and an active memory state (Shafi and others 2003). Such a result must be treated with caution because different classes of excitatory and inhibitory neurons play distinct roles during working memory and may increase or decrease their firing rates in response to a stimulus (further discussed below). Pooling all respons-

Fig. 6. Stability of persistent activity as a function of the AMPA:NMDA ratio at the recurrent excitatory synapses. *A–D*, Temporal course of the average firing rate across a subpopulation of cells selective to the presented transient input, for different levels of the AMPA:NMDA ratio. As the ratio is increased, oscillations of a progressively larger amplitude develop during the delay period, which eventually destabilize the persistent activity state. *E*, Snapshot of the activity of the network in (*C*) between 3 and 3.5 seconds. *Top*, Average network activity. *Bottom*, Intracellular voltage trace of a single neuron. *Inset*, Power spectrum of the average activity of the network, showing a peak in the γ (40 Hz) frequency range. Persistent activity is stable even in the presence of synchronous oscillations. Adapted with permission from Renart, Brunel, and others (2003).



es together may therefore be misleading and does not argue against a rate code.

The question of temporal coding in the spiking patterns of prefrontal cortical neurons was recently addressed by a temporal-statistics analysis (Compte and others 2003). The results revealed that most single units of monkey prefrontal cortex during the mnemonic delay can be well approximated by a purely random, Poisson process that contains no systematic temporal patterns of firing. A smaller proportion of prefrontal neurons exhibit burst discharges. The coefficient of variation of prefrontal interspike intervals is typically near or larger than

1, indicating a high degree of irregularity of delay period neural discharges, consistent with a network mechanism for persistent activity sustained by stochastic synaptic bombardments. Rhythmicity is rarely visible in spike trains of single prefrontal cells during working memory (Compte and others 2003). It is possible that the network might display coherent oscillations detectable only in the population level, for example, reflected in local field potential measurements summing responses from large numbers of neurons, whereas single cells are highly stochastic (Pesaran and others 2002; Brunel and Wang 2003). Regardless of whether oscillations are

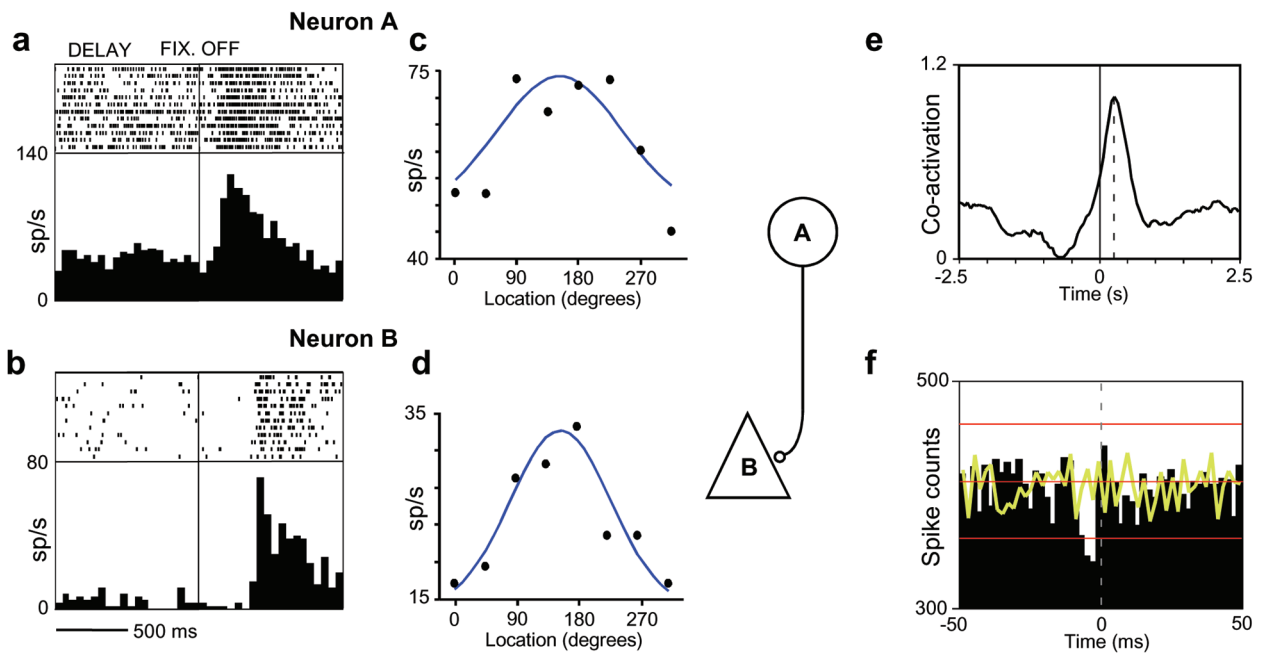


Fig. 7. An example of an inhibitory interaction detected through simultaneous recordings from two microelectrodes. *a–b*, Responses of two neurons recorded 0.3 mm apart. *c–d*, The neurons' spatial tuning, computed in the saccade period. *e*, Coactivation function, indicating the time lag that produced the maximum temporal overlap of the two neurons' responses, shows a 250-ms lag. *f*, Cross-correlation histogram revealing a trough, offset from time zero, consistent with direct inhibition from neuron A onto neuron B. From Constantinidis and others (2002), with permission.

present, there is little doubt that synchronous firing arises between prefrontal neurons during working memory, as shown by simultaneously recorded pairs of single units from behaving monkeys (Constantinidis and Goldman-Rakic 2002). In a rodent study of delayed spatial task, simultaneous recording from many (>20) single prefrontal neurons by multiple-contact electrodes (tetrodes) suggests that working memory could be maintained in a spatio-temporal firing pattern propagating around the network, in which any given cell needs only to fire at a high rate episodically rather than tonically throughout the memory period (Baeg and others 2003). This result, if confirmed by future work especially with primates, would offer a new picture about the dynamic organization of a working memory network. Progress in this direction necessitates the development of techniques for simultaneous recording of large numbers of single neurons or imaging of spatio-temporal firing patterns in the working memory cortical network of behaving monkeys.

Memory Fields Are Shaped by Inhibition

Prefrontal cortical neurons have large, often bilateral memory fields, which are, however, spatially distinct; they are centered at specific spatial locations and are typically flanked by inhibitory surrounds. Inhibition is difficult to detect in neurophysiological recordings, as the baseline discharge rate of pyramidal neurons is low and the inhibitory effect of a remembered stimulus can

easily go unnoticed. Nonetheless, clear examples of inhibitory fields away from a neuron's preferred location have been demonstrated in neurophysiological recordings (Funahashi and others 1989). A recent population analysis of a large neuronal database confirmed that the discharge rate after the presentation of a memorandum at a location diametric to a neuron's preferred location has an overall suppressive effect below the level of background activity (Constantinidis and Goldman-Rakic 2002). A direct demonstration of the role of inhibition has been provided by micro-iontophoretic application of GABA antagonists *in vivo*. Such negation of inhibitory inputs expands the size of the neurons' memory fields, unmasking excitatory zones that were suppressed during normal neuronal function (Rao and others 2000). Inhibitory interactions have also been demonstrated by means of simultaneous recordings and cross-correlation analysis, which also indicated that interneurons inhibit pyramidal neurons active at different time points of the behavioral task (Fig. 7), or exhibiting dissimilar spatial receptive fields (Constantinidis and others 2002).

Pyramidal and nonpyramidal neurons tend to exhibit distinct action potential waveforms and rates of discharges, making it possible to differentiate them in extracellular recordings *in vivo* (Wilson and others 1994; Constantinidis and Goldman-Rakic 2002). It has been thus possible to examine the properties of inhibitory neurons themselves during the maintenance of information in memory. Interneurons receive inputs from nearby pyramidal neurons, and they too exhibit sus-

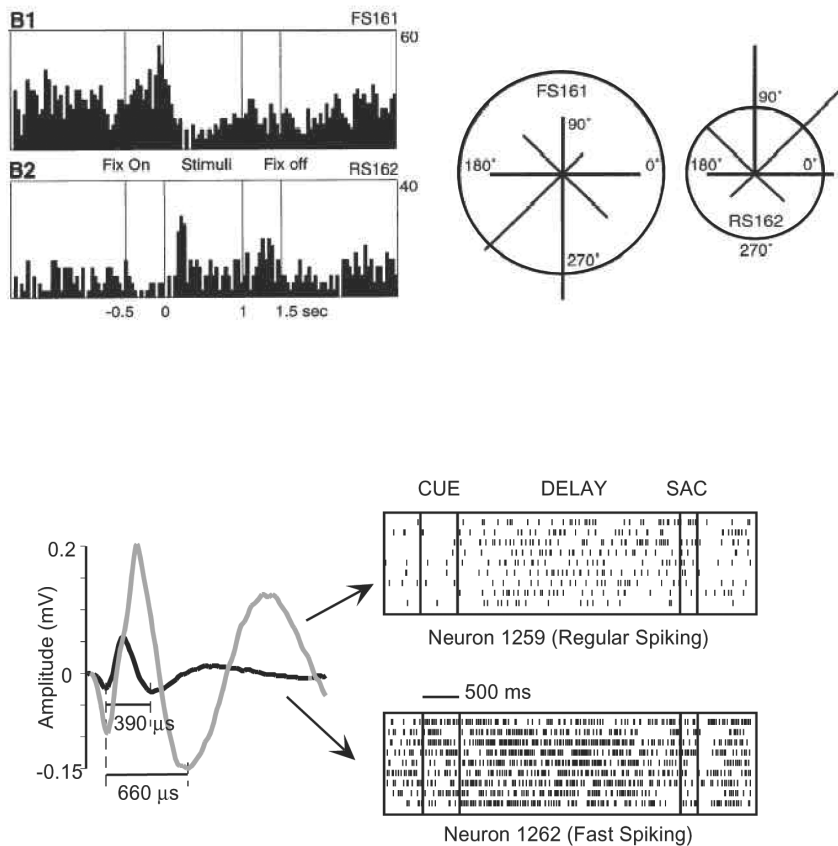


Fig. 8. Responses of putative inhibitory interneurons during the execution of the delayed response task. *Top*, inverted tuning of an interneuron (top histogram and left polar plot) relative to a pyramidal neuron (bottom histogram and right polar plot), recorded in sequence, 0.2 mm apart. The activity of the interneuron is depressed below the baseline during the delay period following presentation of the cue that evokes the best response of the pyramidal neuron (from Wilson and others 1994, with permission). *Bottom*, elevated firing rate is observed for an interneuron (bottom raster plot) and a pyramidal neuron (top raster plot) after presentation of the cue in a location that evoked the best response for both neurons, which were recorded simultaneously from electrodes 0.2 mm apart. Data from Constantinidis and Goldman-Rakic (2002).

tained responses and spatially tuned memory fields. Initial reports from sequential microelectrode recordings within 0.4 mm of each other suggested that interneurons display inverted tuning relative to pyramidal neurons (Fig. 8); interneuron discharges were found to decrease below the baseline during the maintenance in memory of a stimulus in the preferred location of nearby pyramidal neurons (Wilson and others 1994). Later results, based on simultaneous recordings from the same electrode or separate electrodes 0.2 to 0.3 mm apart, indicated that nearby pyramidal neurons and interneurons are tuned to similar spatial locations and demonstrate persistent elevation of neuronal activity (Rao and others 1999; Constantinidis and Goldman-Rakic 2002). Pyramidal cells and interneurons recorded at longer distances from each other may be tuned to opposing spatial locations. Neurons with suppressed responses below the baseline now appear to constitute a distinct subclass of interneurons, as suggested by computational modeling studies. Spatially tuned, sustained activity can be achieved by a network architecture in which nearby pyramidal cells and interneurons show similar selectivity, whereas further separated pyramidal cells and interneurons display opposite tuning (Fig. 9A). A diversity of inhibitory neurons within each cortical module cooperate to provide synaptic inhibition, with different inhibitory neurons

exhibiting different patterns of excitation. A most recent study proposes a theoretical framework for how three major subclasses of interneurons conspire to subserve spatial working memory (Fig. 9C). In this model, inverted tuning, which was originally thought as a defining property of prefrontal interneurons, is displayed by a distinct subclass of interneurons, possibly corresponding to calbindin immunoreactive cells (Wang, Tegner, and others 2004).

The importance of inhibition in the spatial working memory can be illustrated by noting that localized persistent activity can be achieved without any recurrent excitation at all. Instead, significant background external excitation that drives all neurons to fire at relatively high rates, offset by feedback cross-directional inhibition, can sculpture the tuning of activity in a network, allowing interneurons to suppress those excitatory cells that are selective for the cue stimulus (Fig. 9B). Such a network architecture may be the basis of persistent activity that encodes the head direction of an animal during spatial navigation (Sharp and others 2001).

Spatial Working Memory and Mental Illness

Cognitive processes that involve spatial working memory are compromised by a number of mental illnesses,

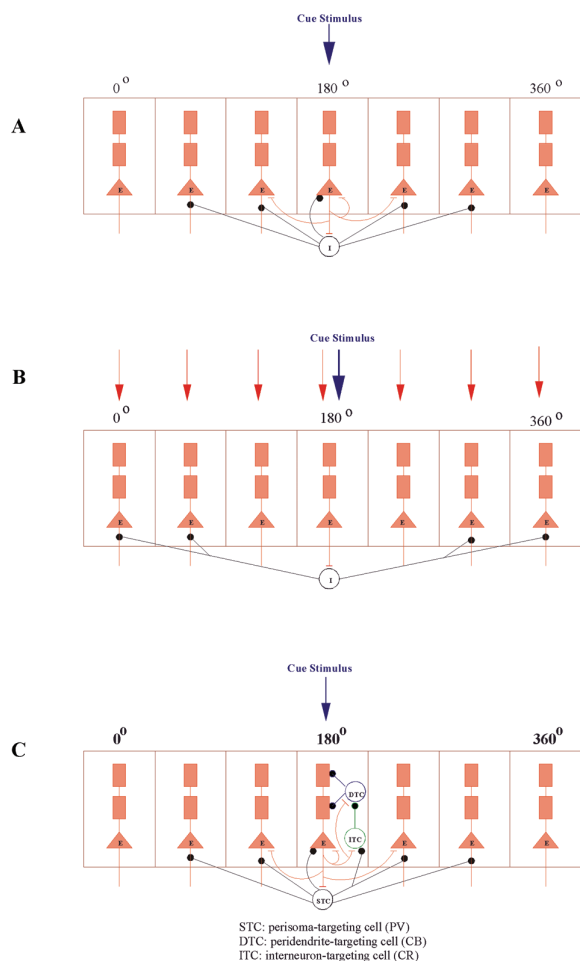


Fig. 9. Three network circuit schemes for spatially tuned persistent activity patterns. *A*, Local recurrent excitation sustains elevated firing in a group of cells, whereas iso-directional inhibition of broader projection extent suppresses excitatory cells on the flanks of the hill of activity. *B*, Tonic external inputs provide uniform drive to the entire excitatory cell population, and cross-directional feedback inhibition gives rise to spatial localization of persistent activity. *C*, Coordinated operation by three subtypes of inhibitory cells in a spatial working memory network. Perisoma-targeting (parvalbumin-containing [PV]) cells provide lateral inhibition, as in (*A*). Within a column, calbindin-containing (CB) interneurons target the dendrites of excitatory neurons, whereas calretinin-containing (CR) interneurons preferentially project to CB cells. Excitation of a group of excitatory cells recruits locally CR neurons, which sends enhanced inhibition to CB neurons, leading to dendritic disinhibition of the same excitatory cells. (*C*) is taken from Wang, Tegner, and others (2004), with permission.

including schizophrenia (Park and Holzman 1992), obsessive compulsive disorder (Purcell and others 1998), major depressive disorder (Murphy and others 2003), and chronic alcoholism (Sullivan and others 1993).

Spatial working memory impairment has been most extensively studied in schizophrenia. Positive symptoms of schizophrenia include delusions, hallucinations, thought disorders, and attentional impairments, and they respond well to typical antipsychotic drugs. Negative

symptoms (absence of normal traits) include affective and motivational deficits, emotional and social withdrawal, disorganized speech, and anhedonia. Schizophrenic patients exhibit impaired performance in spatial working memory tasks that involve eye or manual movements toward the remembered direction of a visual target presented a few seconds earlier or that require them to keep track of the locations of visual stimuli presented or sampled in sequence (Park and others 1995; Pantelis and others 1997). Schizophrenic patients are similarly impaired in antisaccade tasks, requiring an eye movement in the direction opposite to a visual target, and to smooth-pursuit eye movements, tracking a moving visual stimulus (Ettinger and others 2004; Reuter and others 2004). Impairment of spatial working memory performance has been observed in patients with both negative and positive symptoms of schizophrenia, including those with psychosis, those who are medicated and unmedicated, those in the acute phase of illness or in relapse, and even in undiagnosed relatives of schizophrenic patients (Park and others 1995; Carter and others 1996; Park and others 1999; Wood and others 2003). Given the strong linkage between schizophrenia and spatial working memory, performance in spatial working memory tasks has been considered a potential predictive indicator and a marker for the genetic liability to the disease (Fuller and others 2002; Gasperoni and others 2003; McGorry 2003; Niendam and others 2003). The link between working memory and schizophrenia may be the consequence of prefrontal malfunction giving origin to both diminished ability to maintain information in memory and a host of other cognitive distortions. On the other hand, working memory impairment may be a contributing cause of the cognitive defects (Goldman-Rakic 1994).

Why and how spatial working memory is impaired in schizophrenic patients cannot be truly answered at a fundamental level without a deep understanding of the underlying cellular and circuit mechanisms. For example, when the inhibitory circuit organization in the prefrontal cortex is elucidated, it will become clear why particular kinds of defects in cortical interneurons cause behavioral impairments (Lewis and others 2003). Another important example comes from recent progress in studies of dopamine modulation of spatial working memory. Schizophrenia is associated with changes in dopamine innervation and action. The fact that the frontal lobe receives a much more prominent dopaminergic innervation compared to the parietal or occipital areas involved with spatial stimulus representation has also led to speculation that unique aspects of memory maintenance associated with the prefrontal cortex are dopamine dependent.

The effects of dopamine are complex and in many ways remain unclear. Direct injections of dopamine agonists in the prefrontal cortex of monkeys performing a memory task were shown to degrade behavioral performance at the spatial location encoded by the injected site, suggesting a possible inhibitory role of dopamine (Sawaguchi and Goldman-Rakic 1991). However, finer

studies of dopamine agonist micro-iontophoresis in the prefrontal cortex revealed excitatory effects at low concentrations and a dose-dependent effect (Williams and Goldman-Rakic 1995). Dopamine application in prefrontal slice preparations increases the excitability of pyramidal neurons, at least in the superficial cortical layers (Henze and others 2000). On the other hand, dopamine can decrease the presynaptic efficacy of neurotransmission onto pyramidal neurons in layer 5 (Gao and others 2001), and it may even have opposite effects on different synapses of the same neuron: It has been shown to increase the efficacy of inhibitory synapses targeting the dendritic tree, while decreasing the inhibitory effect of perisomatic synapses (Gao and others 2003). Functionally, using micro-iontophoresis in behaving monkeys, it was found that different subtypes of dopamine receptors mediate distinct effects on neural activities responsible for different epochs of the task: D1 receptors affect memory storage during the delay, whereas D2 receptors modulate the neural activity during the behavioral response at the end of the trial (Wang, Vijayraghavan, and others 2004). As a result of the multiple actions of dopamine, episodic hypo- and hyperactivity of the prefrontal cortex may coexist in the same schizophrenic patient in the course of the illness (Seamans and Yang 2004).

Although the effects of dopamine are complex, they are consistent with the idea that dopamine increases the signal-to-noise ratio of activity representing a remembered stimulus (Camperi and Wang 1998; Durstewitz and others 2000; Brunel and Wang 2001; Cohen and others 2002). Enhancement of dendritic inhibition during the maintenance of memory could be an effective mechanism of filtering distracting, sensory information (Wang and others 2004).

Conclusions

In summary, thanks to a highly interdisciplinary approach combining *in vitro* and *in vivo* electrophysiology and computational modeling, there has been significant progress in our understanding of the cortical basis of spatial working memory. However, we are still faced with many challenges ahead. Functional questions about the organization of the prefrontal cortex and its spatial working memory function remain unanswered. Little is known about the precise role of NMDA receptors to excitatory reverberation, the respective roles of and the interplay between prefrontal and parietal cortices, and the continuous nature of spatial encoding at the neural level. Progress on these issues will help to arrive at a deep understanding of the circuit mechanisms of spatial working memory and shed light into the cellular origins of memory impairments associated with schizophrenia and other mental disorders.

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