The Frontal Lobes

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A microcircuit model of prefrontal functions: Ying and Yang of reverberatory neurodynamics in cognition

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1 Introduction

In contrast to neural systems responsible for sensory processing or motor behavior, the prefrontal cortex is a quintessentially ''cognitive'' structure. A bewildering gamut of complex higher brain processes depend on prefrontal cortex. It is thus a particularly challenging quest to elucidate the neurobiology of prefrontal functions at the mechanistic level. Patricia S. Goldman-Rakic voiced this difficulty in 1987:

> Unlike largely sensory and motor skills, the mnemonic, associative, and command functions of the mammalian brain have eluded precise neurological explanation. The proposition that cognitive function(s) can be localized to specialized neuronal circuits is not easy to defend because the neural interactions that underlie even the most simple concept or solution of an abstract problem have not been convincingly demonstrated. Also it does not seem possible to conceptualize in neural terms what it means to generate an idea, to grasp the essentials of a situation, to be oriented in space and time, or to plan for long-range goals. Furthermore we are still learning how to formulate the structure-function problem in a way that can lead to fruitful experimentation, theory building, or modeling in terms of neural systems or synaptic mechanisms.

Since these words were written, some of the impediments have begun to yield ground, partly thanks to the development of novel techniques linking cognitive functions with underlying neural processes. The advent of functional magnetic resonance imagining (fMRI) has opened up a window with which brain activity can be probed and dissected during behavior. Therefore, internal representations and processes that are not necessarily reflected by overt motor responses can now be directly observed and quantitatively analyzed. Stimulated by a confluence of experimental psychology, computer science, clinic neurology, and brain imaging, theory building in cognitive science has evolved from

predominantly ''conceptual models'' (in words and box diagrams) to more quantitative ''connectionist'' neural network models (Dehaene & Changeux, 1995; Cohen *et al.*, 1996; O'Reilly *et al.*, 1999; O'Reilly & Munakata, 2000). Meanwhile, neurobiologists have developed laboratory paradigms that combine psychophysics and neuronal recordings with behaving animals, especially nonhuman primates. While an alert monkey performs a cognitive task (such as working memory, perceptual discrimination, selection of motor response), psychophysical data are collected to quantitatively measure the animal's performance. At the same time and under the same conditions, spike firing activities of individual neurons are recorded from identified brain areas and linked to the animal's behavior (for reviews, see Parker & Newsome, 1998; Romo & Salinas, 2000; Schall, 2001; Pasternak & Greenlee, 2005). Therefore, in many cases, a quantifiable relationship can be established between specific aspects of behavior and spike firing activity of single cells at the spatial resolution of microns and the temporal resolution of milliseconds.

Yet, correlations are not explanations. To build a neurobiological foundation of cognition, we need to understand network behavior underlying higher brain functions in terms of the biophysics of neurons and synapses, microcircuit anatomy, and collective neural dynamics. Past decades have seen tremendous progress in our understanding of the ''hardware'' of cortex and its plasticity. The vast amount of information gained from these advances has helped our efforts in a mechanistic understanding of sensory processing such as orientation selectivity in primary visual cortex, and long-term plasticity such as development of barrels in somatosensory cortex. By contrast, relatively little has been firmly established regarding cellular mechanisms of higher cognitive functions. This situation is changing in recent years, when neuroscientists of various subfields begin to join force in studying prefrontal cortex (Wang & Goldman-Rakic, 2003). The question must be raised: can cognitive functions, such as working memory and decision-making, be described and explained in terms of what we know about the brain: be it the rich repertoire of electroresponsiveness of single neurons (Llinas, 1988), intricate active properties of neuroral dendrites (Magee *et al.*, 1998), dynamics of synaptic connections between individual neurons (Markram *et al.* 1998; Abbott & Regehr, 2004), and microcircuit wiring connectivity (Somogyi *et al.*, 1998; Douglas & Martin, 2004)? In this chapter, I will explore this question from a computational perspective. At the interface between cognitive science and neurobiology, realistic modeling offers a valuable approach for at least two reasons. First, existing experimental methods are limited in linking neural processes observed in behaving animals with the underlying cellular mechanisms; models can serve to bridge these different levels. Second, cognitive functions involve cortical circuits that are strongly recurrent.

Predicting behaviors of such nonlinear systems with positive and negative feedback loops is not easy or even possible by intuition alone, a mathematical framework based on dynamical systems theory and computational methods is needed.

I will discuss models of prefrontal cortex that are constructed based on the known cortical anatomy and electrophysiology. To be concrete, I have chosen to focus on a cardinal prefrontal function which is nevertheless simple enough for detailed mechanistic analysis at the microcircuit level. I will thus devote the bulk of this chapter to delayed response behavior that engages working memory. As we shall see later, the same models designed for working memory are also suitable for decision-making processes. Finally, I will argue that theory of microcircuit neural dynamics provides a framework for understanding how alternations at the molecular level (e.g. deficits in glutamate, GABA, dopamine transmission) give rise to impaired network behaviors associated with mental diseases such as schizophrenia.

2 Mnemonic persistent neural activity

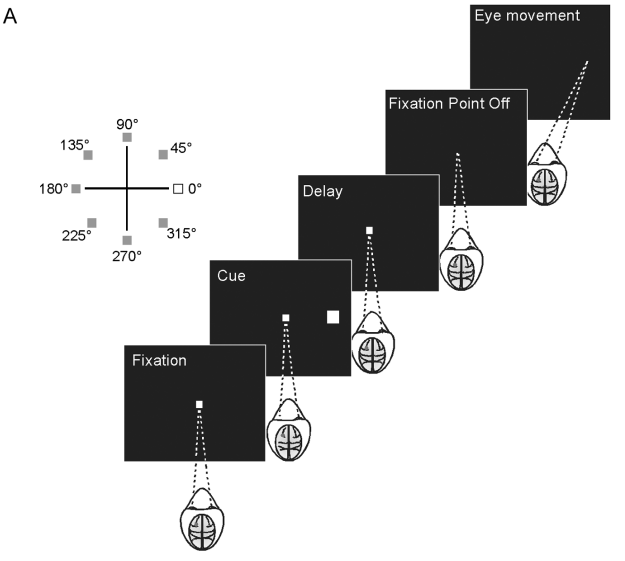
In delayed response tasks (Hunter, 1913), the sensory stimulus and motor response are separated by a brief delay period, during which time the sensory information must be actively held in mind by the subject. The behavior goes beyond simple stimulus-response reflexes and engages active short-term memory or "working memory." In the 1930s, C. F. Jacobsen (Jacobsen 1936) demonstrated that lesion of prefrontal cortex in monkeys induced specific deficits in delayed response tests. It is worth noting that such deficits did not occur with temporal lobe lesions, a result that was confirmed by later monkey lesion studies (Bachevalier *et al.*, 2002) and in consonance with evidence from the human clinical literature (H. M. had essentially intact active short-term memory) (Milner, 1972). Subsequent work by K. H. Pribram, H. E. Rosvold, M. Mishkin and others substantiated Jacobsen's finding and established delayed response tasks as a paradigm of choice for studying prefrontal cortex (see Curtis & D'Esposito [2004] for a recent critical review). The delayed response task is simple compared to other cognitive tasks, and thus offers a paradigm amenable to rigorous experimentation for studying prefrontal function in the laboratory.

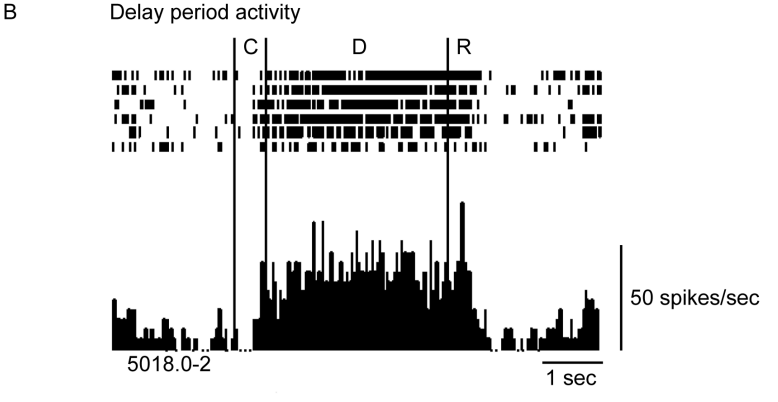
When single neuron recordings from awake monkeys became possible Fuster and Alexander (1971) discovered that, during delayed response tasks, cells in prefrontal cortex displayed elevated spike discharges throughout the delay period while the animal was required to maintain sensory information internally in the absence of sensory stimulation. Persistent neural activity was immediately recognized as candidate neural correlate of working memory. Over the last

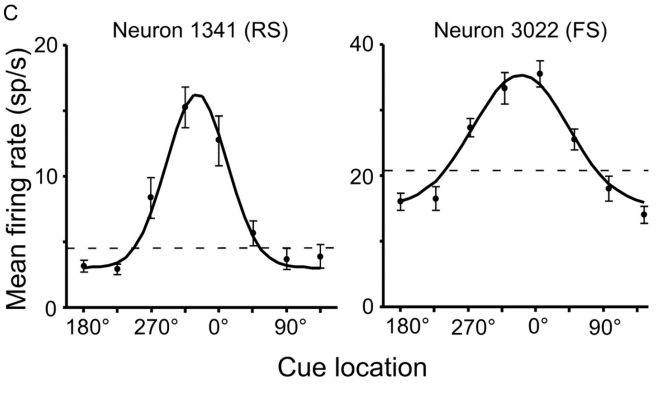
35 years, there has been a large body of work documenting mnemonic persistent activity in prefrontal cortex (Funahashi *et al.*, 1989; Miller *et al.*, 1996; Rainer *et al.*, 1998; Romo *et al.*, 1999), posterior parietal cortex (Gnadt & Andersen, 1988; Chafee & Goldman-Rakic, 1998), inferotemporal cortex (Fuster & Jervey, 1982; Miyashita, 1988), and basal ganglia (Hikosaka & Wurtz, 1983).

An especially elegant paradigm is the spatial delayed oculomotor task (Figure 4.1A). Using this task Funahashi *et al.* (1989) found that many neurons in the dorsolateral prefrontal cortex, including and surrounding the principal sulcus, and in the frontal eye field, exhibited mnemonic persistent activity during the delay period (Figure 4.1B). Remarkably, the delay activity of a recorded neuron was selective for preferred spatial cues (the cell's ''memory field''), and this selectivity could be quantified by a bell-shaped tuning curve (Figure 4.1C). The discovery of ''memory fields'' demonstrated an internal representation of visuospatial information in the prefrontal cortex. This representation is observable and can be quantitatively described in terms of a Gaussian tuning of persistent delay activity at the single-cell level. However Gaussian tuning is commonplace among cortical neurons. Perhaps the best known example is orientation selectivity in primary visual cortex, the mechanisms of which have been extensively studied in cortical physiology (Sompolinsky & Shapley, 1997; Ferster & Miller, 2000). Thus, the question of prefrontal microcircuitry underlying working memory could be formulated in cellular and synaptic terms (Goldman-Rakic, 1995; Wang, 2001): what are the excitatory-inhibitory synaptic mechanisms for the formation of memory fields? What are the microcircuitry properties of the prefrontal cortex, such as local horizontal connections, that give rise to persistent activity?

The persistence time (up to 10 s) of sustained firing activity during working memory is orders of magnitude longer than the biophysical time constants (tens of milliseconds) of fast electrical signals in neurons and synapses. For this reason, persistent activity is believed to be generated by feedback dynamics, or reverberation, in a neural circuit (Lorente de Nó, 1933; Hebb, 1949; Amit, 1995). The characteristic horizontal connections found in the superficial layers II–III of the dorsolateral PFC may provide the anatomical substrate for such a recurrent circuit (Levitt *et al.*, 1993; Kritzer & Goldman-Rakic, 1995). This idea is made precise in theoretical work where persistent activity is described as ''dynamical attractors'' (Wilson & Cowan, 1973; Amari, 1977; Amit, 1995; Wang, 2001). The mathematical term ''attractor'' simply means any self-sustained and stable state of a dynamical system, such as a neural network. For example, according to this picture, in a working memory system, the spontaneous state and stimulus-selective memory states are assumed to represent multiple attractors, such that a memory state can be switched on and off by transient inputs.


A
Eye movement
Fixation Point Off
Delay
Cue
Fixation
90°
135°
45°
180°
0°
225°
315°
270°


B
Delay period activity
C
D
R
50 spikes/sec
5018.0-2
1 sec


C
Neuron 1341 (RS)
Neuron 3022 (FS)
Mean firing rate (sp/s)
20
10
0
40
20
0
180°
270°
0°
90°
Cue location

This formulation is plausible, inasmuch as stimulus-selective persistent firing patterns are dynamically stable and approximately tonic in time (e.g. across a delay). However, it remains unproven that attractor networks can be realized in the brain. To determine the realistic synaptic properties and circuit dynamics that are required for a robust network-induced persistent activity, biologically-constrained models of persistent activity were needed, which became possible only recently thanks to the advances in quantitative neurophysiology (Wang, 2001; Major & Tank, 2004). Broadly speaking, feedback mechanisms underlying reverberation can either arise from recurrent network dynamics (Amit & Brunel, 1997; Lisman *et al.*, 1998; Wang, 1999; Durstewitz *et al.*, 2000b; Compte *et al.*, 2000; Seung *et al.*, 2000; Brunel & Wang, 2001; Miller *et al.*, 2003), or from intrinsic membrane/intracellular dynamics of single cells (Camperi & Wang, 1998; Egorov *et al.*, 2002; Koulakov *et al.*, 2002; Goldman *et al.*, 2003; Loewenstein & Sompolinsky, 2003). This chapter will mostly deal with circuit mechanisms but, as we shall see, network functions strongly depend on the biophysical properties of single cells, even though the latter alone are not sufficient to account for mnemonic persistent activity.

3 A biophysically based model of working memory

A network model for the Funahashi experiment of spatial working memory is illustrated in Figure 4.2A. The key feature is the preeminence of recurrent connections (''loops'') between neurons, so that a cell receives not only external stimulation (via afferents from upstream neurons) but also inputs from other cells within the same microcircuit (via ''horizontal'' connections). A commonly assumed network architecture is the so-called ''Mexican-hat'': localized recurrent excitation between pyramidal cells with similar preference to spatial cues, and broader inhibition mediated by interneurons. Models of synapses and single cells

Figure 4.1 (A) 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 (inset at left). After a delay period of a few seconds, the disappearance of the fixation light spot signals the end of the delay. At that moment the monkey must make an accurate saccadic eye movement to the location where the cue was shown before the delay period, in order to collect a liquid reward. (B) Activity of a single prefrontal neuron, exemplifying persistent discharges during working memory. (C) Tuning curves of mnemonic delay period activity in a regular spiking putative pyramidal cell (left) and a fast-spiking putative interneuron (right). ([A–C] are adopted from Constantinidis & Wang [2004]; Funahashi *et al.* [1989], and Constantinidis & Goldman-Rakic [2002] respectively, with permission.)

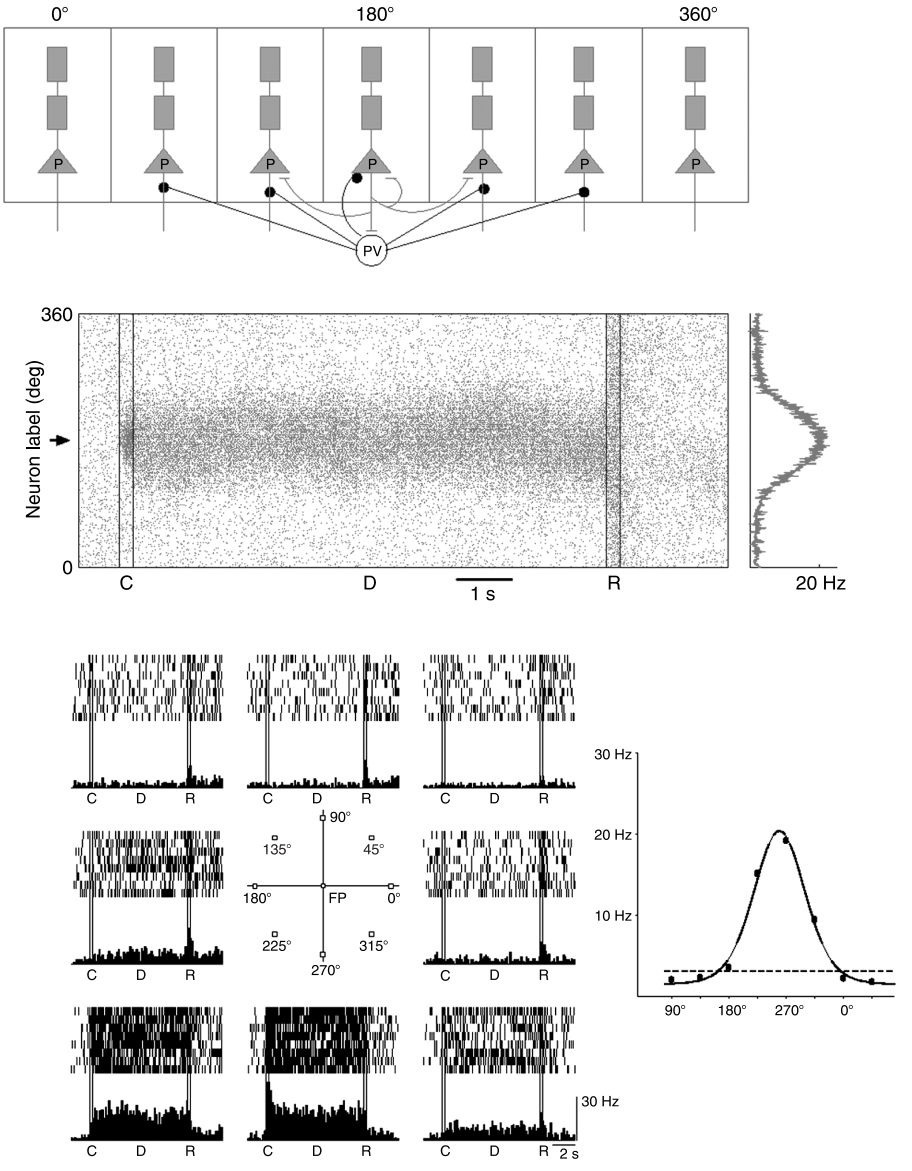


Figure 4.2 Working memory maintained by a spatially tuned network activity pattern (a "bump attractor"). Top: model architecture. Excitatory pyramidal cells are labeled by their preferred locational cues (0° to 360°). Pyramidal cells of similar preferred cues are connected through local E-to-E connections. Interneurons receive inputs from excitatory cells and send feedback inhibition by broad projections. Middle: a network simulation of delayed oculomotor response experiment. C: cue period; D: delay period; R: response period. Pyramidal neurons are labeled along the y-axis according to their preferred cues. The x-axis represents time. A dot in the rastergram indicates a spike of a neuron whose preferred location is at y, at time x. Note the enhanced and localized neural activity that is triggered by

are calibrated quantitatively by cortical electrophysiological studies. This is important: as we will discuss below, even though network function is determined by the collective dynamics of many thousands of neurons, the emergent population behavior depends critically on the properties of single cells and synapses.

Figure 4.2B shows a model simulation of the delayed oculomotor task (Compte *et al.*, 2000; Renart *et al.*, 2003) (for movie presentation of this model, go to http://wanglab.ccs.brandeis.edu). Initially, the network is in a resting state in which all cells fire spontaneously at low rates. A transient input (in this case at 180°) drives a subpopulation of cells to fire at high rates. As a result they send recruited excitation to each other via horizontal connections. This internal excitation is large enough to sustain elevated activity, so that the firing pattern persists after the stimulus is withdrawn. Synaptic inhibition ensures that the activity does not spread to the rest of the network, and persistent activity has a bell shape (''bump attractor''). At the end of a mnemonic delay period the cue information can be retrieved by reading out the peak location of the persistent activity pattern; and the network is reset back to the resting state. In different trials, a cue can be presented at different locations. For example, across eight cue presentations the firing activity of a single cell (Figure 4.2C) can be compared with the single-unit recording data from monkey's prefrontal cortex (Funahashi *et al.*, 1989). At the network level, each cue triggers a persistent firing pattern of the same bell-shape but peaked at a different location. A spatial working memory network thus requires a continuous family of ''bump attractors,'' each encoding a potential location (Ben-Yishai *et al.*, 1995; Camperi & Wang, 1998; Compte *et al.*, 2000; Renart *et al.*, 2003; Song & Wang, 2005). The instantiation of such a continuous attractor can be rendered robust by regulatory homeostatic mechanisms in a biophysically realistic cortical network in spite of cellular heterogeneities (Renart *et al.*, 2003).

Thus, this biologically constrained model captures salient experimental observations from behaving monkeys. What lessons have we learned from such a model?

Figure 4.2 (contd.) a transient cue stimulus and persists during the delay period. The population firing profile, averaged over the delay period, is shown on the right. Bottom left: firing activities of a single cell when the cue was shown in one of the eight locations indicated in the center diagram. This neuron exhibits an elevated persistent activity in the delay only for one direction (270°), and is suppressed relative to intertrial spontaneous activity in the upper visual field. Bottom right: the delay period tuning curve shows the average discharge rate during the delay period (circles), together with a Gaussian fit of the data. The horizontal line indicates average intertrial spontaneous activity. Data provided by A. Compte. (For a color version of this figure, please see the color plate section.)

4 Excitation-inhibition balance

A conspicuous feature of our network model is multistability: a resting state coexists with a number of stimulus-selective memory states, so that transient inputs lead to switching between self-sustained network firing patterns, or "attractors" (Figure 4.3). When the attractor network scenario for working memory was tested with biophysically realistic models, it was recognized that such a system with strong recurrent loops is prone to instability. For instance, the resting state should be stable to small perturbations due to noisy spontaneous neural firing, in spite of strong excitatory recurrency. This is realized by a tight balance between excitation and inhibition (E-I balance), like Ying and Yang in ancient Chinese philosophy. In fact, in the resting state, feedback inhibition is slightly larger than excitation, hence the overall recurrent input to a neuron is inhibitory (Figure 4.4A) and spontaneous spike firing is driven by random background external inputs. Interestingly, in a memory state in which stronger reverberatory excitation is recruited to sustain an elevated firing rate, synaptic inhibition increases proportionally with excitation (Figure 4.4B–C); this dynamically maintained E-I balance contributes to controlling the firing rates and preventing runaway excitation. Other experimental and theoretical work suggests that a fixed E-I balance, regardless of changing neuronal firing rates, may be

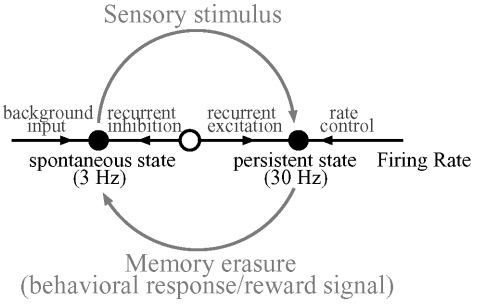


Figure 4.3 Schematic illustration of the biophysics underlying an attractor dynamics. An attractor is a neural firing state that is stable to perturbations: when a small input perturbs the network to a lower or higher activity level, there is a "restoring force" to bring the network back to the attractor state. In this case, the spontaneous state is stabilized from below by background inputs, and from above by feedback synaptic inhibition. A sufficiently powerful sensory stimulus can drive a cell assembly to "escape" from the spontaneous state, and after the stimulus is withdrawn the system settles in one of the active memory states at an elevated firing rate. The persistent activity state is stabilized from below by excitatory reverberation, and from above by various negative feedback "rate control" mechanisms. Finally, a behavioral response or reward signal can turn the network off and erase the memory. (Adopted from Wang [2001] with permission.) (For a color version of this figure, please see the color plate section.)

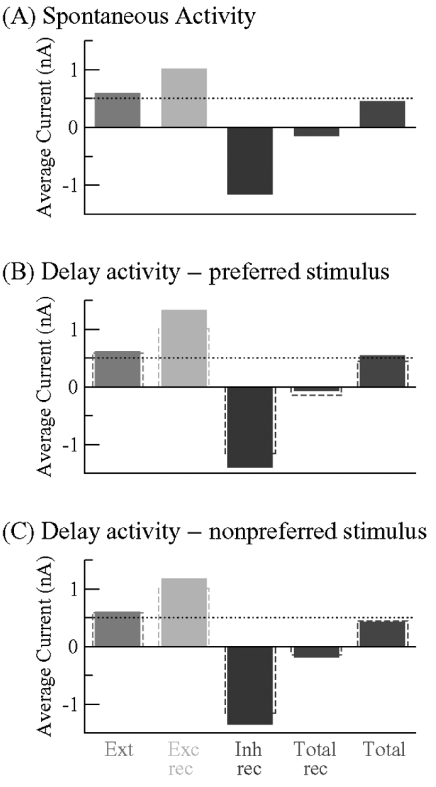


Figure 4.4 Balanced excitation and inhibition in the spatial working memory model (same as in Figure 4.2). Various components of synaptic current in a single cell during spontaneous activity (top), during delay activity following presentation of a preferred stimulus (middle), and during delay activity following presentation of a nonpreferred stimulus (bottom). The dotted line indicates the value of excitatory synaptic currents needed to reach the (deterministic) firing threshold. In the two lower panels, the dotted boxes indicate the value of the corresponding component during spontaneous activity, to show the differences between delay and spontaneous activity. Background external inputs are superthreshold. Recurrent circuit is dominated by inhibition (brown) over excitation (orange) in the spontaneous state, so that the net recurrent synaptic current is hyperpolarizing (blue). During delay activity both recurrent excitation and inhibition are larger and dynamically balance each other, in such a way that the overall synaptic excitation becomes slightly larger following a preferred stimulus (leading to persistent activity at an elevated rate) than after a nonpreferred stimulus. (For a color version of this figure, please see the color plate section.)

a general characteristic of cortical network dynamics (Shadlen & Newsome, 1994; Shu *et al.*, 2003; Compte *et al.*, 2003b; Liu, 2004).

The balancing act of recurrent excitation and inhibition may contribute to an explanation for the highly irregular spike discharges in prefrontal cells

(Compte *et al.*, 2003a). On the other hand, we found that the E-I balance often manifests itself in the form of coherent network oscillations, typically in the gamma (40 Hz) frequency range (Wang, 1999; Compte *et al.*, 2000; Tegnér *et al.*, 2002) (Figure 4.5). This is because fast excitation followed by slower inhibition is a common recipe for rhythmogenesis in neural networks (Wilson & Cowan, 1972; Wang, 2003). Synaptic inhibition mediated by $GABA_A$ receptors is typically about 3–5 times slower than fast synaptic excitation mediated by AMPA receptors, the latter having a decay time constant of a few milliseconds (Hestrin *et al.*, 1990b; Xiang *et al.*, 1998). Modeling studies showed that coherent oscillations resulting from an interplay between AMPAR-mediated excitation

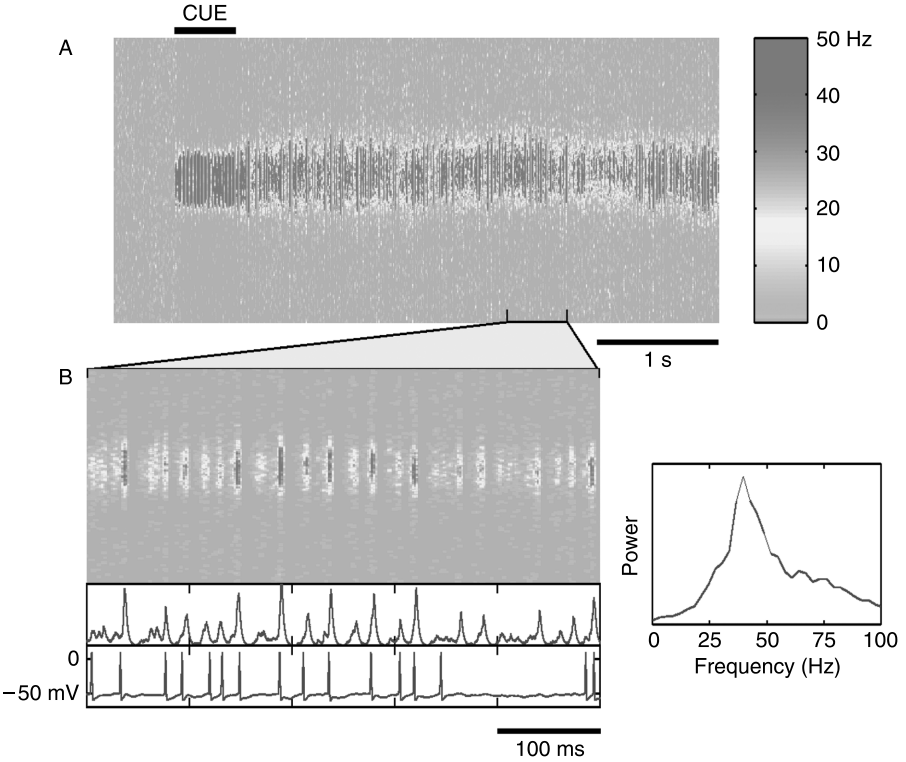


Figure 4.5 Gamma oscillations during working memory. (A) Spatiotemporal firing pattern of a spatial working memory model same as in Figure 4.2 (with slightly different parameters) except that firing rates are color-coded. (B) 500-ms blowup of (A) to show synchronous oscillations in the spatiotemporal activity pattern (top), the local field potential (middle) and membrane potential of a single neuron (bottom). On the right is shown the power spectrum of the local field, demonstrating a large peak at about 40 Hz. (Adopted from Compte *et al.* [2000] with permission.) (For a color version of this figure, please see the color plate section.)

and $GABA_AR$-mediated inhibition have a preferred frequency range around 40 Hz (Brunel & Wang, 2003). This theoretical finding suggests that synchronous 40-Hz oscillations may be observed in mnemonic persistent activity, a notion that has found some experimental support (Pesaran *et al.*, 2002). In this view, fast γ rhythms may be a characteristic sign of the engagement of strongly reverberatory cortical circuits in cognition and memory.

5 The importance of being slow: role of NMDA receptors

A system with fast positive and slow negative feedbacks, both powerful, is prone to dynamical instability. Persistent activity is often disrupted in the middle of a delay period, thereby the memory is lost (Wang, 1999; Compte *et al.*, 2000; Tegnér *et al.*, 2002; Renart *et al.*, 2003). The same destabilization problem is present if negative feedback is instantiated by spike-frequency adaptation (McCormick *et al.*, 1985) or short-term synaptic depression (Markram *et al.*, 1998; Abbott & Regehr, 2004). Such instability does not occur, if the excitation is sufficiently slow, when compared to negative feedback, i.e. when recurrent synapses are primarily mediated by NMDA receptors (time constant 50–100 ms) (Wang, 1999; Compte *et al.*, 2000). Moreover, the slow NMDAR unbinding to glutamate gives rise to saturation of the NMDA synaptic current with repetitive stimulation at high frequencies (Figure 4.6). As a result further increase in neural firing rates does not lead to a larger excitatory drive, and the explosive positive feedback is curtailed. Therefore it helps to control the firing rate in a persistent activity state (Wang, 1999).

A specific suggestion from modeling work, then, is that in a working memory microcircuit, *if persistent activity is primarily sustained by synaptic reverberation*, local excitatory synapses should have a sufficiently high NMDA/AMPA ratio. How high is high enough? The answer depends on the details of network biophysics and connectivity. For instance, the time constant of a synaptic current depends on the subunit composition of its receptors. If $GABA_A$-receptor-mediated inhibition is unusually fast in a working memory circuit, instability due to the time constant mismatch with AMPA-receptor-mediated excitation would be less severe, and the required NMDA/AMPA ratio would be lower (Tegnér *et al.*, 2002). Furthermore, if a slow ion channel in single cells contributes to positive feedback, then less NMDA/AMPA ratio would also be needed, as shown in Figure 4.7 (Tegnér *et al.*, 2002). The general idea is that positive feedback should not be too fast compared to negative feedback, when both are powerful in a working memory circuit. This remains true if persistent activity is generated not by a synaptic mechanism, but by intrinsic membrane dynamics of single neurons.

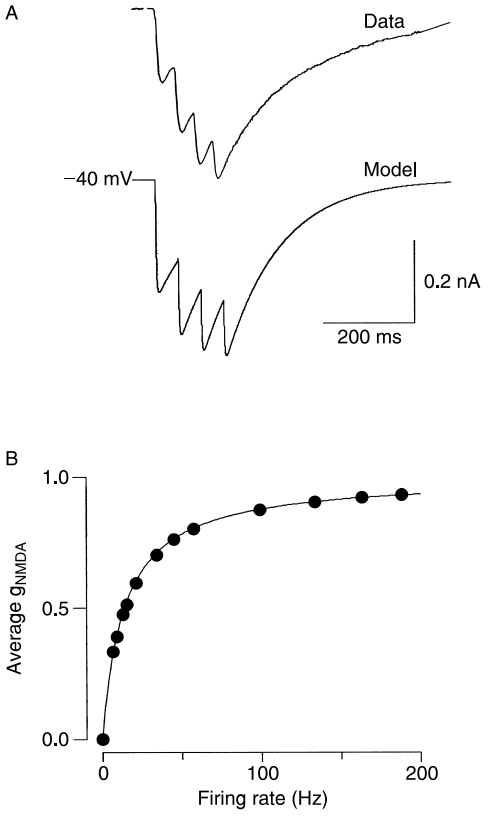


Figure 4.6 Temporal summation of the NMDAR-mediated excitatory postsynaptic currents (EPSCs). (A) NMDAR-mediated EPSCs elicited by four stimuli, when the membrane potential is clamped at −40 mV. Upper panel: data from a pyramidal neuron in CA1 of the rat hippocampus (redrawn from [Hestrin *et al.*, 1990b] with permission). The stimulus is at 25 Hz. Note the significant summation and saturation. These properties are mediated postsynaptically by the NMDARs, since they are absent in the non-NMDR-mediated EPSCs recorded in the same cell at −100 mV. Lower panel: NMDAR-mediated EPSCs produced by a model synapse in response to a stimulus at 20 Hz. (B) The average NMDAR-mediated EPSC as function of stimulus frequency. (Adopted from Wang [1999] with permission.)

6 Stimulus selectivity and resistance against distractors

As I discussed earlier, like Ying and Yang, reverberatory excitation should be balanced by synaptic inhibition to ensure proper function of a working memory circuit. Synaptic inhibition plays a critical role in sculpturing stimulus selectivity of mnemonic persistent firing patterns, in consonance with the observation that $GABA_A$ receptor antagonists resulted in the loss of spatial tuning of prefrontal neurons during a delayed oculomotor task (Rao *et al.*, 2000). Note that it is useful to distinguish between "feedforward" inhibition (from GABAergic cells driven

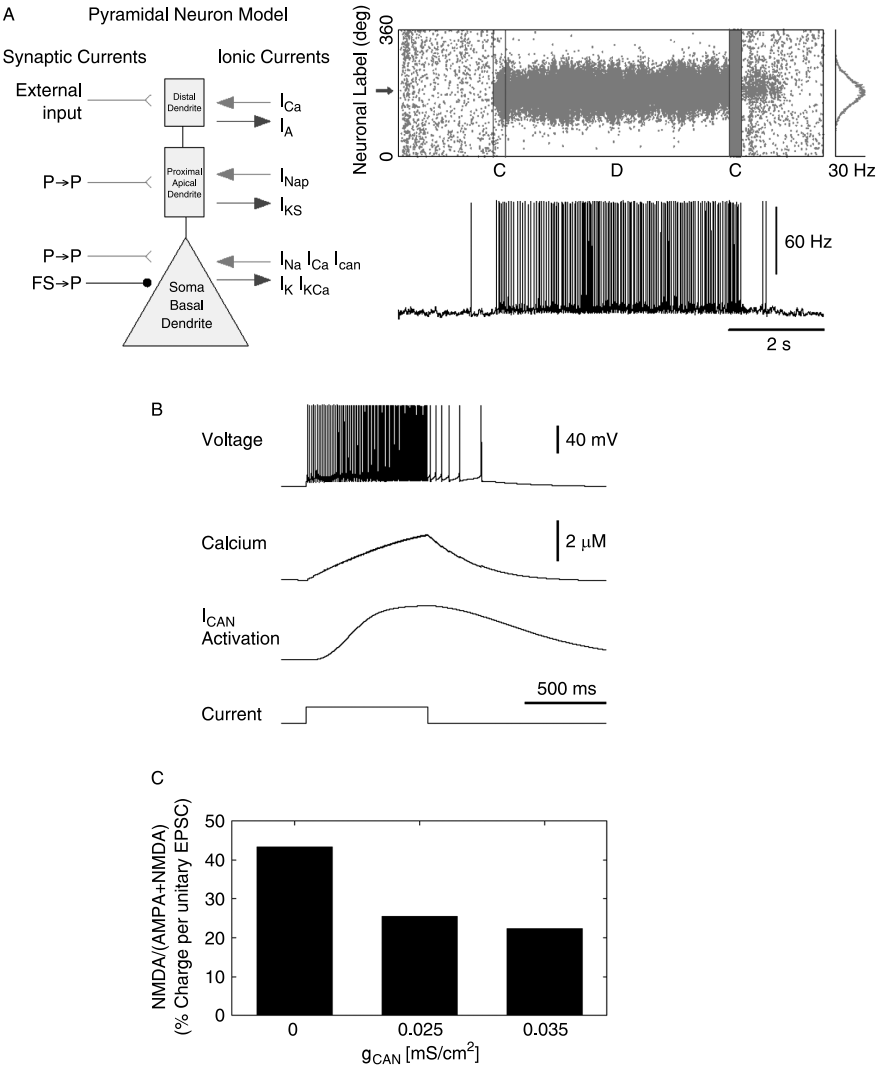


Figure 4.7 A spatial working memory model, with single neurons endowed with three compartments (soma, proximate and distal dendrites) and a number of voltage-gated ion channels. (A) Left: schematic single pyramidal cell model; right: spatiotemporal network activity (top) and membrane potential of a single cell (bottom) in a simulation of the delayed oculomotor experiment. Data provided by J. Tegnér (2002). (B) Electroresponsiveness of an isolated pyramidal cell model with a nonselective cation current I_{Can}. The calcium-dependent activation of I_{Can} is slow, leading to a ramping-up time course of the neural response. A few action potentials are still fired after stimulus extinction, in parallel with a slow deactivation of I_{Can}. Notice that the neuron is not bistable; it returns to stable resting state. (C) Slow ionic currents (here I_{Can}) reduce the minimum level of NMDAR that is required for sustained delay activity. Further increase in g_{Can} renders the neuron intrinsically bistable (not shown). (Adopted from Tegnér *et al*. [2002] with permission.) (For a color version of this figure, please see the color plate section.)

by external afferents) and "feedback" inhibition (from those predominantly driven by pyramidal cells within the same local circuit). For instance, it has been proposed that bell-shaped tuning of orientation in primary visual cortical neurons is constructed by a feedforward inhibitory mechanism (Ferster & Miller, 2000), or feedback (recurrent) mechanisms (Sompolinsky & Shapley, 1997), or a combination of both. Because stimulation is absent during a delay period, inhibition underlying selectivity of mnemonic activity is presumably driven by local pyramidal cells, hence of the feedback type. According to Compte *et al.* (2000), inhibitory cells that sculpture spatial selectivity of pyramidal cells should have broader tuning curves, a prediction that was later confirmed by experiments (Constantinidis & Goldman-Rakic, 2002) (Figure 4.1, bottom panel).

Another key aspect of memory maintenance, in which inhibition plays an important role, is resistance against distractors: while behaviorally relevant information is actively held in mind, irrelevant sensory stimuli should be denied entrance to the working memory system. In delayed response experiments using intervening stimuli (distractors), mnemonic activity has been shown to be easily disrupted by distractors in inferotemporal neurons but not in prefrontal neurons (Miller *et al.*, 1996). Similarly, delay period activity in posterior parietal cortex appears to be sensitive to distractors (Powell & Goldberg, 2000; Constantinidis & Procyk, 2004). Therefore the evidence, albeit not conclusive, suggests that although multiple cortical areas exhibit delay period activity, mnemonic neural signals in prefrontal cortex may persist when those in the temporal lobe and parietal lobe are lost, so that behaviorally relevant information is maintained in the brain in spite of distractors. This observation at the single-cell level suggests a candidate basis for the proposal that prefrontal cortex is a pivotal part of the attention network that focuses brain resources on selective information (Mesulam, 2000).

What enables prefrontal cortex to resist distracting stimuli? A gating mechanism may be involved in deciding which stimulus is behaviorally relevant and thus should be held in working memory (Cohen *et al.*, 1996, 2002). On the other hand, it is desirable that a working memory circuit be endowed with mechanisms to filter out, "by default," external inputs that constantly bombard our senses. We found that synaptic inhibition naturally gave rise to this capability (Compte *et al.*, 2000; Brunel & Wang, 2001). This is because, in a memory delay period, active neurons recruit inhibition which project to the rest of the network. Consequently, those cells not encoding the initial cue are less excitable than when they are in the resting state (see Figures 4.2 and 4.7A), hence less responsive to distracting stimuli presented during the delay. For spatial working memory, the impact of a distractor depends on its strength (saliency) and the distance to the memorized cue (Figure 4.8A). More generally, we found that the network's

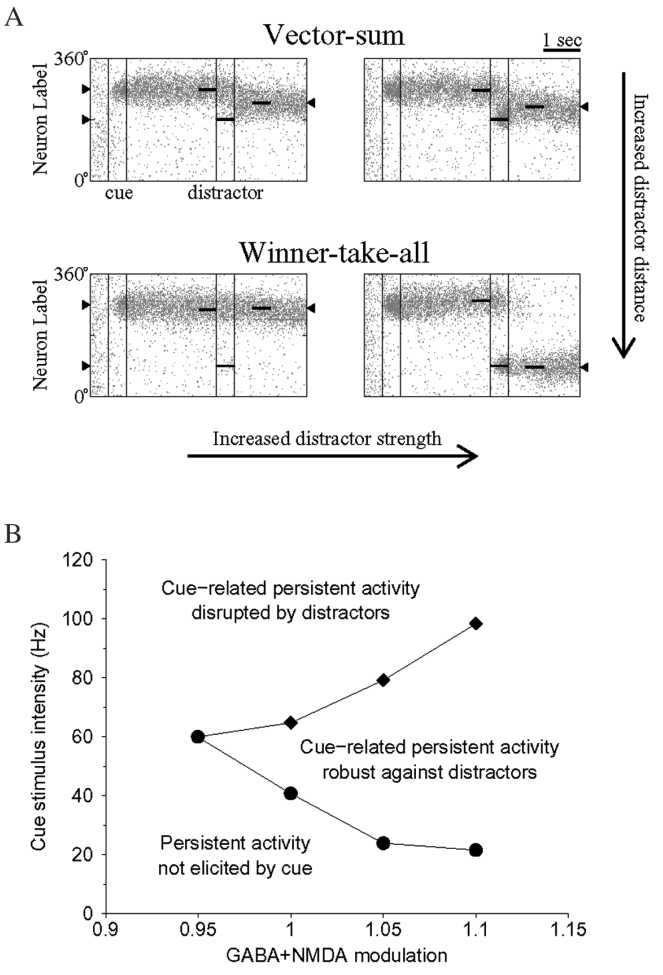


Figure 4.8 Resistance against distractors. (A) In the spatial working memory model, the initial cue (upper arrow on the left) triggers persistent activity centered at 180°. During the delay, a second cue (distractor) is shown briefly (lower arrow on the left). When the distractor is close to the initial stimulus, the network performs a vector sum so that the final remembered cue is half-way between the two (arrow on the right). On the other hand, when the distractor is far away from the initial stimulus, the network operates in a winner-take-all regime, so that the final remembered cue is either the initial stimulus or the distractor, depending on the strength of the stimuli. (B) Behavior of an object working memory model as function of dopamine modulation of NMDAR-mediated recurrent excitation and $GABA_AR$ inhibition (x-axis) and amplitude of cue stimulation (y-axis). A very weak stimulus (initial cue) cannot elicit persistent activity (lower left region), whereas a powerful stimulus (distractor) can override recurrent dynamics and disrupt delay activity (upper left region). The desirable behavior (robust persistent activity in spite of distractors) (middle right region) is sensitive to dopamine modulations. (Adopted from Brunel & Wang [2001] with permission.) (For a color version of this figure, please see the color plate section.)

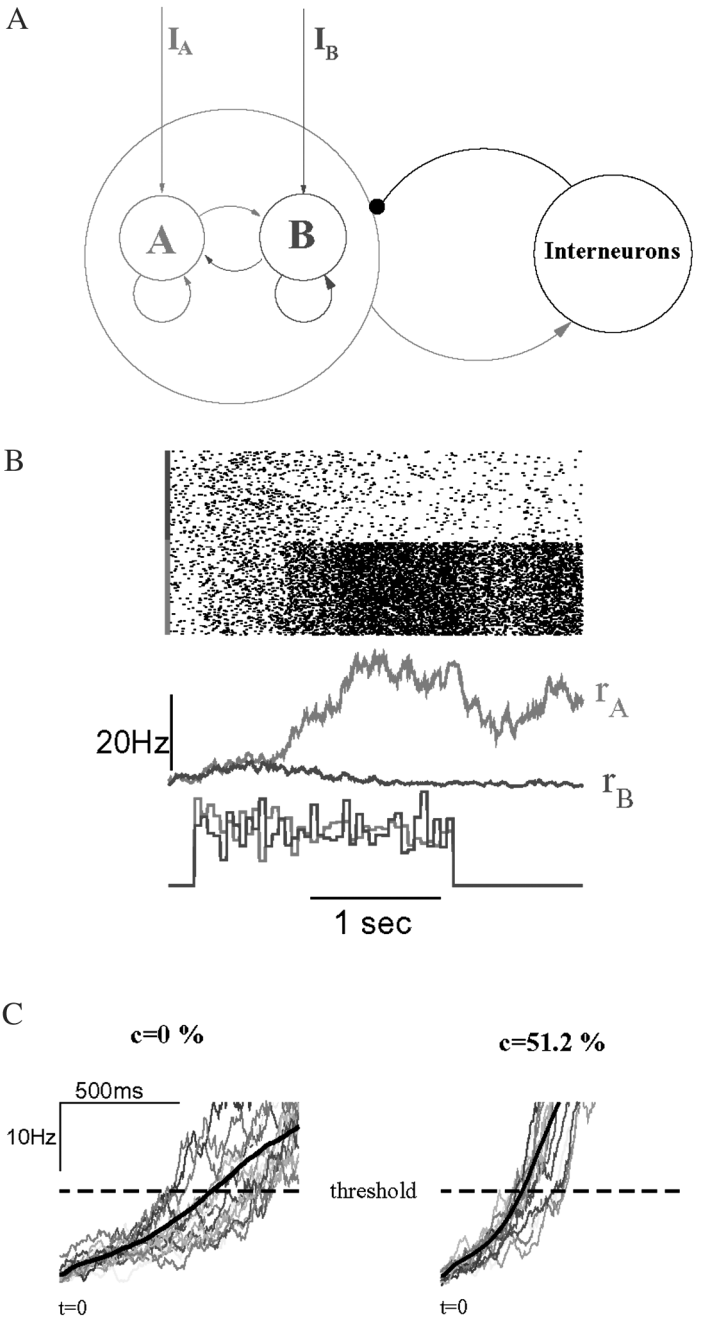


Figure 4.9 (A) A simple model for two-alternative forced-choice tasks. There are two pyramidal cell groups, each of which is selective to one of the two directions (A = left, B = right) of random moving dots in a visual motion discrimination experiment. Within each pyramidal neural group there are strong recurrent excitatory connections which can sustain persistent activity

ability to ignore distractors is sensitive to modulation of recurrent excitation and inhibition (Figure 4.8B). This finding has important implications for dopaminergic signaling in prefrontal cortex (see below).

7 Decision-making

So far, I have focused on delayed response tasks. We have seen that this approach provides a valuable probe into the detailed mechanisms of prefrontal microcircuitry. However, currently there is a heated debate as to whether prefrontal function should be conceptualized by internal representation (memory maintenance) or processes (decision-making, executive control) (Miller & Cohen, 2001; Curtis & D'Esposito, 2003; Wood & Grafman, 2003). Unexpectedly, it turns out that the same models originally developed for working memory can account for decision-making processes as well (Wang, 2002; Machens *et al.*, 2005). An example is shown in Figure 4.9 from model simulations of visual motion discrimination (Newsome *et al.*, 1989; Parker & Newsome, 1998). In this two-alternative forced choice task, monkeys are trained to make a judgment about the direction of motion (say, left or right) in a near-threshold stochastic random dot display, and to report the perceived direction with a saccadic eye movement. Neurons in posterior parietal cortex (Shadlen & Newsome, 2001; Roitman & Shadlen, 2002) and prefrontal cortex (Kim & Shadlen, 1999) were found to exhibit firing activity correlated with the animal's perceptual choice. We used the same model designed for working memory to simulate this decision experiment; with the only difference that for delayed response task only one stimulus is presented, whereas for perceptual discrimination tasks conflicting sensory inputs are fed into competing neural subpopulations in a decision circuit (Figure 4.9A). Our model accounts for not only salient characteristics of the observed decision-correlated neural activity (Figure 4.9B–C), but also

Figure 4.9 (contd.) triggered by a transient preferred stimulus. The two neural groups compete through feedback inhibition from interneurons. The motion coherence is expressed as $c = (\mu_A - \mu_B)/(\mu_A + \mu_B)$, where μ_A and μ_B are the mean values of inputs IA and IB. (B) A network simulation with zero coherence. Top to bottom: network spiking raster, population firing rates r_A and r_B, stochastic inputs I_A and I_B. Note the initial slow ramping (time integration) and eventual divergence of r_A and r_B (categorical choice). (C) In reaction time simulations, when one of the two neural groups reaches a fixed threshold (15 Hz) of population firing activity, the decision is made and the deliberation or decision time is read out. The decision time is longer and more variable at low coherence (left) than at high coherence (right). (Adopted from Wang [2002] with permission.) (For a color version of this figure, please see the color plate section.)

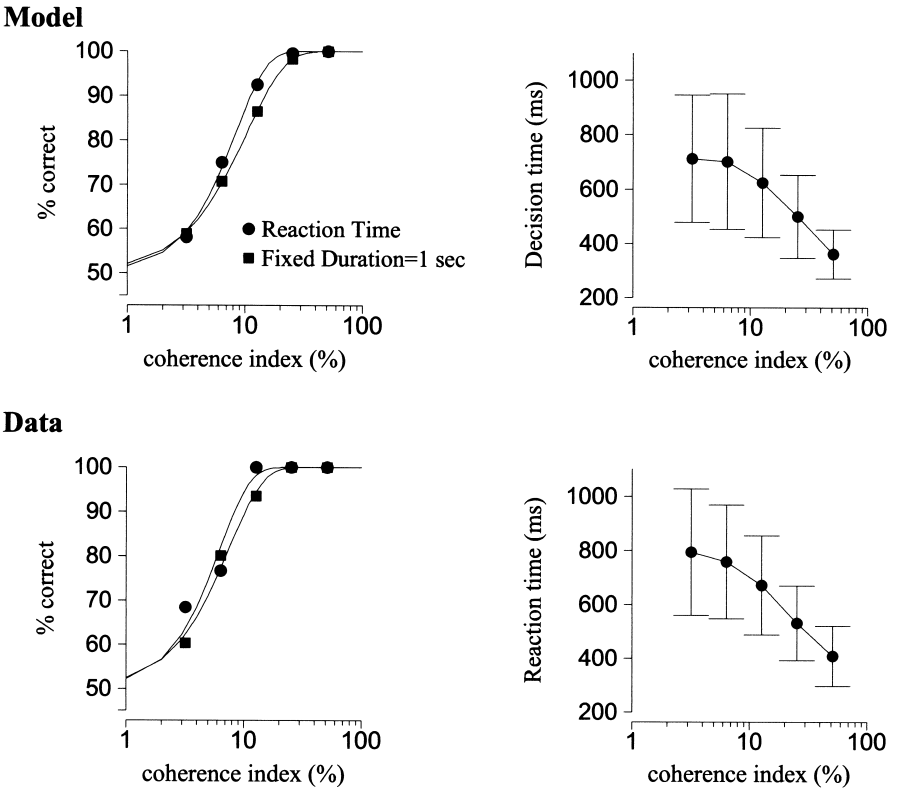


Figure 4.10 Top: left panel: psychometric functions for the reaction time stimulation (circle) and with fixed stimulus duration of 1 s (square); right panel: average decision time as function of the coherence level, ranging from 200 ms at high c to 800 ms at low c. At very low coherence there is a saturation. Note the large standard deviation of decision time, especially at low coherence. (Adopted from Wang [2002] with permission.) Bottom: monkey's behavioral data reproduced with permission from Roitman & Shadle (2002).

quantitatively for the animal's behavioral performance (psychometric function and reaction times) (Figure 4.10).

8 Distinct features of prefrontal microcircuitry

Quantitative differences breed qualitatively different behaviors. That a cortical area exhibits a new type of behavior does not necessarily mean that the circuit must possess unique biological machineries completely different from other areas. Hence, persistent activity may be generated in the prefrontal cortex when the strength of recurrent excitation (mediated by AMPA+NMDA receptors combined) exceeds a critical threshold, whereas this may not be the case for a sensory area such as the primary visual cortex. Based on our modeling results,

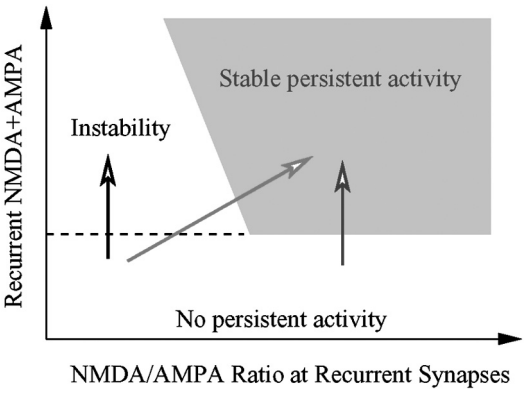


Figure 4.11 Schematic depiction of the dependence of stable persistent activity on both sufficiently strong recurrency (y-axis) and large NMDA/AMPA ratio at local excitatory synapses (x-axis). A circuit that does not exhibit persistent activity may be endowed with this ability by strengthening excitatory connections while preserving a relatively large NMDA/AMPA ratio (blue arrow). However, an enhancement of recurrency at a low NMDA/AMPA ratio can lead to network dynamical instability (black arrow), in which case the NMDA/AMPA ratio needs to be increased simultaneously (red arrow). (For a color version of this figure, please see the color plate section.)

we can extend this idea and propose that, for stable function of a working memory circuit, the NMDA/AMPA ratio at recurrent synapses should also be above a certain threshold, as illustrated in Figure 4.11. It is important to emphasize that what matters for persistent activity is not the unitary amplitude of EPSCs at resting potential, but the ratio of the average NMDA and AMPA synaptic currents during repetitive neural discharges. This ratio depends on multiple factors such as presynaptic short-term plasticity, postsynaptic summation and saturation and voltage-dependence of the NMDA channel conductance. Further, a relatively high NMDA/AMPA ratio at local synapses can be compatible with a low total NMDA/AMPA ratio in a neuron, for instance if feedforward inputs from outside of the network are predominantly mediated by AMPA receptors. Last but not least, this ratio can be enhanced by neuromodulators, such as dopamine (Chen *et al.*, 2004; Huang *et al.*, 2004; Seamans & Yang, 2004).

Immunochemical analysis revealed a significantly larger amount of mRNA expression of NMDA receptor subunits in prefrontal neurons, compared to primary visual cortical neurons (Figure 4.12). It is unknown whether this simply correlates with a larger number of spines (hence synaptic connections) per pyramidal cell in prefrontal cortex (Elston, 2000). In any event, contribution of NMDA receptors to synaptic transmission locally between prefrontal pyramidal cells remains to be established by direct electrophysiological measurements, e.g. using intracellular recording from connected pairs of neighboring

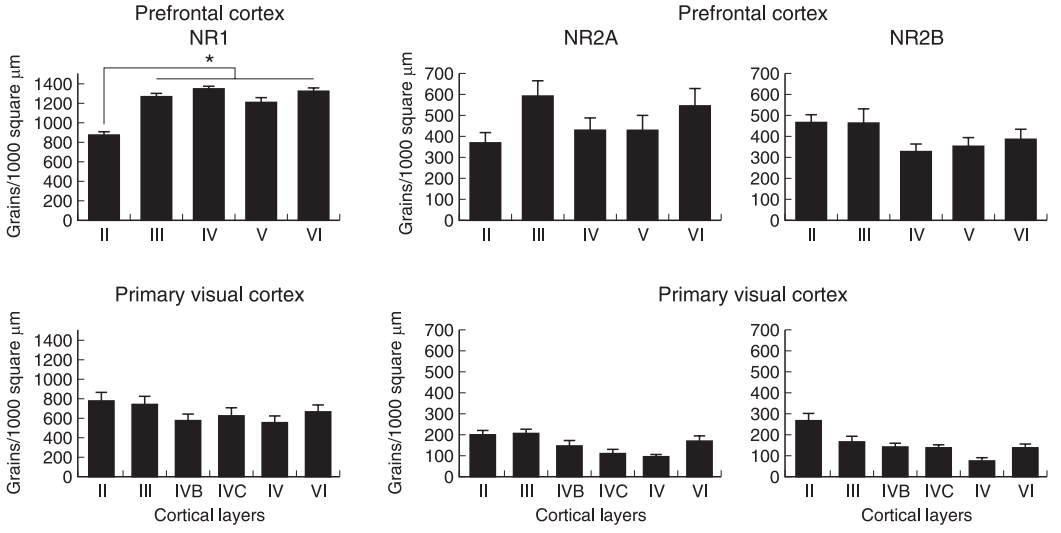


Figure 4.12 mRNA expression of NMDA receptor subunits NR1, NR2A and NR2B in human prefrontal cortex (top) and primary visual cortex (bottom). (Adopted from Scherzer *et al.* [1998] with permission.)

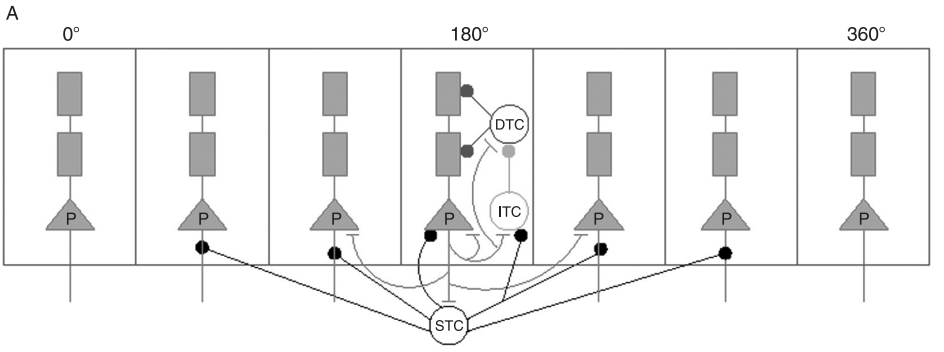
cells in prefrontal slices. On the other hand, iontophoresis can be used to selectively block NMDARs in recorded prefrontal cells of behaving monkeys during working memory (Williams & Goldman-Rakic, 1995; Shima & Tanji, 1998; Wang *et al.*, 2004b). Traditionally, the function of NMDA conductance is almost exclusively emphasized in terms of its role in long-term synaptic potentiation and depression. Thus, an abundance of NMDA receptors could reflect a high degree of plasticity of prefrontal microcircuit, which could subserve learning flexible and adaptive behaviors (Miller & Cohen, 2001; Stuss & Knight, 2002). That may be, but we propose that NMDA receptors also directly mediate slow excitatory synaptic transmission critically important to working memory, and that this may explain why NMDA receptor antagonists produce working memory impairment in healthy human subjects (Krystal *et al.*, 1994). Taken one step further, effects on cognitive behavior by genetic manipulation of NMDARs may also be partly caused by altered short-term memory, in addition to long-term memory.

On the other side of Ying and Yang, prefrontal cortex may also be endowed with specialized inhibitory circuitry. A salient feature of cortical organization is the presence of a wide diversity of GABAergic interneurons, with regards to their morphology, electrophysiology, chemical markers, synaptic connections and short-term plasticity, molecular characteristics (Freund & Buzsaki, 1996; Cauli *et al.*, 1997; DeFelipe, 1997; Kawaguchi & Kubota, 1997; Somogyi *et al.*, 1998; Buzsaki *et al.*, 2004; Markram *et al.*, 2004). How do different

interneuron types work together in prefrontal cortex? To investigate this question, we have extended our model of spatial working memory to incorporate three subclasses of interneurons classified according to their synaptic targets (Wang *et al.*, 2004a). In this model (Figure 4.13A), in addition to widespread inhibition mediated by perisoma-targeting and parvalbumin-containing (PV) interneurons, dendrite-targeting (calbindin-containing, CB) interneurons receive inputs from interneuron-targeting (calretinin-containing, CR) interneurons, leading to an activity-dependent local disinhibition of pyramidal cells.

Note that the three interneuron types in our model should be more appropriately interpreted according to their synaptic targets, rather than calcium-binding protein expressions. For example, PV cells display a variety of axonal arbors, among which the large basket cells (Krimer & Goldman-Rakic, 2001; Kisvarday *et al.*, 2003) are likely candidates for our widely-projecting cells. Similarly, CB interneurons show a high degree of heterogeneity, but some of them (such as double bouquet cells) are known to act locally and preferentially target dendritic spines and shafts of pyramidal cells (DeFelipe, 1997; Somogyi *et al.*, 1998). Finally, although many CR interneurons do project to pyramidal cells (DeFelipe, 1997), anatomical studies show that a subset of CR cells avoid pyramidal cells (Gulyás *et al.*, 1996), at least in the same cortical layer (Meskenaite, 1997), and preferentially target CB interneurons (DeFelipe *et al.*, 1999). It is also possible that axonal innervations of a CR cell project onto pyramidal cells in a different cortical layer, while selectively targeting inhibitory neurons in the same layer (Meskenaite, 1997; Gonchar & Burkhalter, 1999). Whether such selective connection pattern holds true as a general principle can only be settled by further anatomical studies. Moreover, electrophysiological evidence is presently lacking about the preferred innervations of a subset of CR interneurons onto GABAergic cells; progress in this direction would be most welcome.

We found that the disinhibition mechanism, mediated by CR inhibition of CB interneurons, contributes significantly to the formation of memory field, as well as the network's ability to filter out distracting stimuli (Wang *et al.*, 2004a). Interestingly, the distributions of PV, CB and CR interneurons appear to be quite different in macaque monkey prefrontal cortex (Conde *et al.*, 1994; Gabbott & Bacon, 1996) compared to primary visual cortex (Brederode *et al.*, 1990; Meskenaite, 1997) (Figure 4.13B). In the prefrontal cortex the proportions are 24% (PV), 24% (CB) and 45% (CR), respectively, according to Conde *et al.* (1994) and Gabbott and Bacon (1996). Other studies reported different estimates (Kondo *et al.*, 1999; Dombrowski *et al.*, 2001; Elston & Gonzalez-Albo, 2003), presumably due to species differences and technical factors (different cell-counting methods and antibodies used for calcium-binding proteins,



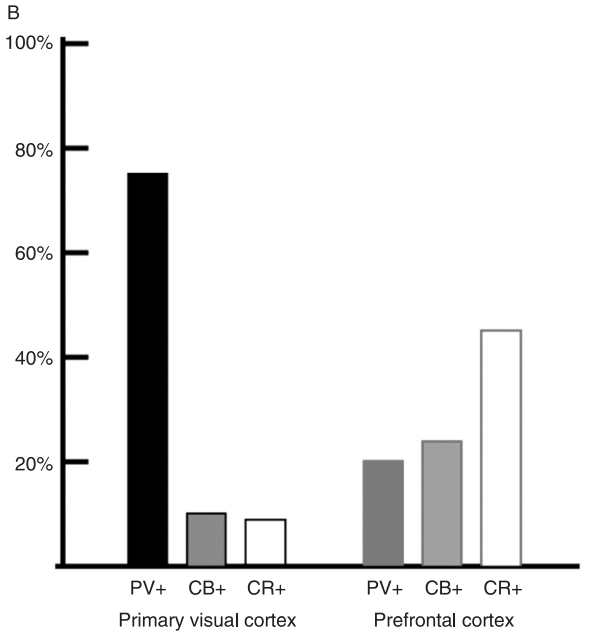


Figure 4.13 (A) A spatial working memory model with three subclasses of GABAergic interneurons. Pyramidal (P) neurons are arranged according to their preferred cues (0 – 360°). There are localized recurrent excitatory connections, and broad inhibitory projections from perisoma-targeting (parvalbumin-containing, PV) fast-spiking neurons to P cells. Within a column, calbindin-containing (CB) interneurons target the dendrites of P neurons, whereas calretinin-containing (CR) interneurons preferentially project to CB cells. Excitation of a group of pyramidal cells recruits locally CR neurons, which sends enhanced inhibition to CB neurons, leading to dendritic disinhibition of the same pyramidal cells. (Adopted from Wang *et al*. [2004] with permission.) (B) Proportional distribution of PV, CB and CR expressing GABAergic cells in primary visual cortex and prefrontal cortex. See text for details. (For a colour version of this figure, please see the colour plate section.)

overlapping CB expression by GABAergic cells and pyramidal neurons, etc). Future work is needed to resolve these discrepancies, and to test the hypothesized disinhibition mechanism and assess whether it may be especially prominent in working memory circuit.

9 Insights into prefrontal dysfunction in schizophrenia

Our modeling work has given rise to a number of specific candidate explanations for frontal lobe dysfunction associated with schizophrenia and other mental disorders.

We showed that impairment of NMDARs at intrinsic prefrontal synapses is detrimental to persistent activity underlying working memory. If borne out, these results may shed insights into why working memory dysfunction similar to that observed in schizophrenic patients can be induced in healthy subjects by subanesthetic doses of ketamine, a noncompetitive NMDA receptor antagonist (Krystal *et al.*, 1994). Postmortem studies showed significant alterations of the NMDAR mRNA expression (Akbarian *et al.*, 1996), but did not reveal abnormality (Healy *et al.*, 1998) or a slight increase (Dracheva *et al.*, 2005) in the AMPAR level. Available information does not yet permit a more precise explanation as to why and how impairment of the NMDA receptor system causes cognitive deficits associated with schizophrenia. It has been previously suggested that impairment can occur outside of prefrontal cortex, such as in hippocampus (Grunze *et al.*, 1996; Jodo *et al.*, 2005; Rowland *et al.*, 2005) or in the dopamine system (Carlsson *et al.*, 2001). Again, functional implications tend to be discussed in the realm of learning and synaptic modification. By contrast, our modeling work suggests a novel scenario focused on the role of NMDARs in persistent activity. Of course, this scenario is compatible with other proposals, given that impairment of NMDARs may not be restricted to a single pathway, and that NMDARs play a major role in long-term synaptic plasticity. These different facets of NMDAR function are also under influence of dopamine modulation (Chen *et al.*, 2004; Huang *et al.*, 2004).

On the other side of Ying-Yang, there is mounting evidence that the dorsolateral prefrontal cortex of schizophrenic patients shows abnormality of selective interneuron subtypes, especially fast-spiking basket and chandelier cells (Lewis *et al.*, 2005). Our theory suggests that this may be the case for two reasons. Modeling work (Compte *et al.*, 2000; Brunel & Wang, 2001; Wang *et al.*, 2004a), in concordance with physiological experiments (Rao *et al.*, 2000; Constantinidis & Goldman-Rakic, 2002), demonstrates that inhibition mediated by fast spiking and broadly projecting interneurons is critical to the stimulus selectivity, hence information specificity, of mnemonic persistent activity. Moreover, fast spiking

GABAergic cells are critical to the generation of coherent gamma (40 Hz) oscillations (Traub *et al.*, 1996; Wang & Buzsaki, 1996; Wang, 2003; Traub *et al.*, 2004), which may contribute to cognitive processes such as feature integration in perception (Singer & Gray, 1995) or selective attention (Fries *et al.*, 2001). Revealingly, gamma oscillations appear to be decreased in schizophrenic brain compared to control subjects (Lee *et al.*, 2003; Spencer *et al.*, 2004). Thus, deficits in synaptic inhibition could impair the quality of information stored in working memory as well as the brain's ability to bind distributed neural activity.

We found that inhibition is also crucial for robust working memory despite ongoing sensory flow. This result provides another insight into how dopamine may affect prefrontal functions (Durstewitz *et al.*, 2000a; Brunel & Wang, 2001). It is known that dopamine acts on prefrontal cortex partly through modulation of gluatamergic and GABAergic synaptic transmissions (see Arnsten [1998] and Seamans & Yang [2004] for reviews). Our modeling showed that a relatively small increase by dopamine of recurrent connections (while preserving the E-I balance) can lead to significant enhancement of the network's resistance against distractors. Conversely, mild impairment of dopamine signaling in the prefrontal cortex can result in behavioral distractibility associated with mental disorders such as schizophrenia. Moreover, according to the disinhibition mechanism (Figure 4.13), dendritic inhibition is reduced locally in activated pyramidal cells, but increased in those pyramidal cells not engaged in encoding the shown stimulus. This mechanism mediated by CB interneurons could serve to filter out distracting stimuli, and that this mechanism is enhanced with a larger dendritic/somatic inhibition ratio (Wang *et al.*, 2004a). A high dendritic/somatic inhibition ratio in a working memory circuit may be hard-wired, for example with a large proportion of CB cells in prefrontal cortex. Alternatively, it can also be dynamically controlled by neuromodulators such as dopamine.

Interestingly, an in vitro work suggests that dopamine D1 receptor activation precisely increases the ratio of dendritic/somatic inhibition onto pyramidal cells in prefrontal cortex (Gao *et al.*, 2003). Using double intracellular recording in prefrontal cortex slices and morphological reconstruction, it was found that bath application of dopamine has a dual effect on the inhibitory synaptic transmission in a pyramidal cell of the prefrontal cortex. Dopamine was found to reduce the efficacy of inhibitory synapses onto the perisomatic domains of a pyramidal cell, mediated by fast-spiking interneurons; whereas it enhances inhibition at synapses from accommodating or low-threshold spiking interneurons that target the dendritic domains of a pyramidal cell (Gao *et al.*, 2003). Our model predicts a specific function for such a dual dopamine action, namely it could boost the ability of a working memory network to filter out behaviorally irrelevant distracting stimuli. Our modeling work (Brunel & Wang, 2001),

as well as brain imaging (Sakai *et al.*, 2002), points to a possible physiological basis of the clinical literature documenting distractibility as a common symptom of frontal lobe damage (Goldman-Rakic, 1987; Fuster, 1988; Mesulam, 2000).

10 Concluding remarks

In this chapter I discussed biophysically based neural modeling that, in concert with experiments, offers a powerful tool for investigating the cellular and circuit mechanisms of mnemonic persistent activity in delayed response tasks. This approach has been used to assess whether the attractor model for working memory and decision-making can be instantiated by biologically plausible mechanisms. Our theoretical work suggests that slow excitatory reverberation underlies persistent activity in working memory and time integration in decision-making (Figure 4.14). A candidate cellular substrate is the NMDA receptors at local recurrent synapses; an alternative/complementary scenario involves intrinsic channels and calcium dynamics in single cells. Recurrent excitation must be balanced by feedback inhibition, which is mediated by several types of GABAergic interneurons. We found that inhibitory circuitry plays a key role in stimulus selectivity (similarly as in sensory areas) and the network's resistance against distracting stimuli (a cardinal requirement for robust working memory), as well as winner-take-all competition in decision-making. These modeling predictions can be tested experimentally, such as by in vitro physiology or iontophoresis of transmitter receptor blockers with behaving nonhuman primates.

We have confined ourselves to models in which working memory storage is maintained by roughly tonic (constant) spike discharges in a neural assembly

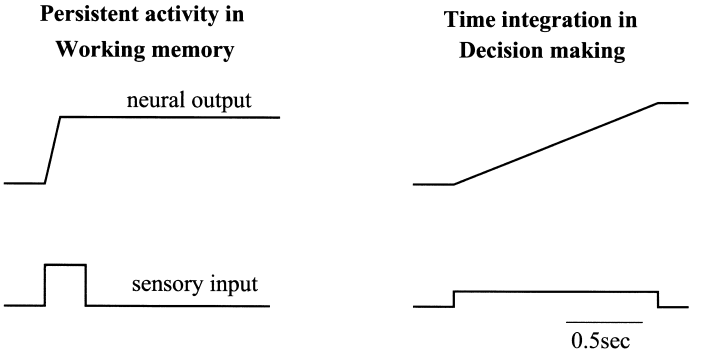


Figure 4.14 Working memory requires neurons to convert a transient input pulse into a self-sustained persistent activity, whereas decision-making involves neuronal ramping activity for accumulation of sensory information. Both types of time integration can be subserved by slow reverberatory dynamics in a recurrent neural network.

across a delay period. However, many cortical cells exhibit delay activity that is not stationary but ramps up or down over time (Fuster, 1988; Chafee & Goldman-Rakic, 1998; Brody *et al.*, 2003). Such ramping activity can conceivably be realized in a two-layer network, in which first-layer neurons show tonic delay activity whereas second-layer neurons slowly integrate inputs from the first-layer neurons in the form of ramping activity (Miller *et al.*, 2003). Moreover, self-sustained network activity can occur as a firing pattern that propagates in a neural network (Sanchez-Vives & McCormick, 2000; Cossart *et al.*, 2003). It remains unclear how the specificity of stored information can be preserved in dynamically moving neural activities (Baeg *et al.*, 2003).

Our emphasis on *internal representations* by no means underestimates the importance of processes such as action selection. Rather, we propose that prefrontal cortex does not simply send out nonspecific "control signals" and that representational information is indispensable to processes. As it turns out, our model is capable of both working memory maintenance and decision-making computations. These results suggest that it may not be a mere coincidence that decision-related neural activity has been found in the same cortical areas that also exhibit persistent activity during working memory (Romo & Salinas, 2000; Schall, 2001). In our model, both working memory and decision-making rely on slow reverberatory dynamics that gives rise to persistent activity and time integration (Figure 4.14), and inhibitory circuitry that leads to selectivity and winner-take-all competition. Thus, we are beginning to unravel the microcircuit properties of a "cognitive" cortical area (such as prefrontal cortex as in contrast to, for example, primary visual cortex) that enable it to serve multiple cognitive functions. At a fundamental level, these studies point to a unified view about why and how "cognitive" cortical area can serve both internal representation (active working memory) and processing (decision, action selection, etc).

Microcircuitry is at a level of complexity ideally suited for bridging the gap between cognitive network functions and the underlying biophysical mechanisms. The delicate balancing act of recurrent excitation and feedback inhibition is at the heart of strongly nonlinear dynamics that underlie cognitive processes in prefrontal cortex. Therefore, ultimately, microcircuit neurodynamics hold the key to a theoretical foundation for neuropharmacology and molecular psychiatry (Harrison & Weinberger, 2005), and a full understanding of mental disorders.

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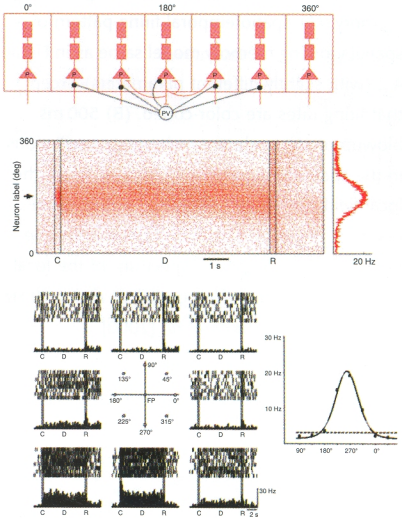


Figure 4.2 Working memory maintained by a spatially tuned network activity pattern (a "bump attractor"). Top: model architecture. Excitatory pyramidal cells are labeled by their preferred locational cues (0° to 360°). Pyramidal cells of similar preferred cues are connected through local E-to-E connections. Interneurons receive inputs from excitatory cells and send feedback inhibition by broad projections. Middle: a network simulation of delayed oculomotor response experiment. C: cue period; D: delay period; R: response period. Pyramidal neurons are labeled along the y-axis according to their preferred cues. The x-axis represents time. A dot in the rastergram indicates a spike of a neuron whose preferred location is at y, at time x. Note the enhanced and localized neural activity that is triggered by a transient cue stimulus and persists during the delay period. The population firing profile, averaged over the delay period, is shown on the right. Bottom left: firing activities of a single cell when the cue was shown in one of the eight locations indicated in the center diagram. This neuron exhibits an elevated persistent activity in the delay only for one direction (270°), and is suppressed relative to intertrial spontaneous activity in the upper visual field. Bottom right: the delay period tuning curve shows the average discharge rate during the delay period (circles), together with a Gaussian fit of the data. The horizontal line indicates average intertrial spontaneous activity. Data provided by A. Compte.

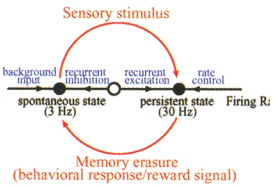


Figure 4.3 Schematic illustration of the biophysics underlying an attractor dynamics. An attractor is a neural firing state that is stable to perturbations: when a small input perturbs the network to a lower or higher activity level, there is a "restoring force" to bring the network back to the attractor state. In this case, the spontaneous state is stabilized from below by background inputs, and from above by feedback synaptic inhibition. A sufficiently powerful sensory stimulus can drive a cell assembly to "escape" from the spontaneous state, and after the stimulus is withdrawn the system settles in one of the active memory states at an elevated firing rate. The persistent activity state is stabilized from below by excitatory reverberation, and from above by various negative feedback "rate control" mechanisms. Finally, a behavioral response or reward signal can turn the network off and erase the memory. (Adopted from Wang [2001] with permission.)

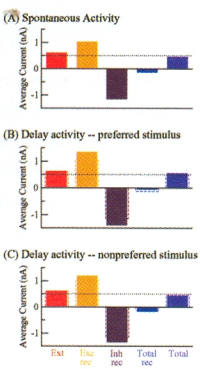


Figure 4.4 Balanced excitation and inhibition in the spatial working memory model (same as in Figure 4.2). Various components of synaptic current in a single cell during spontaneous activity (top), during delay activity following presentation of a preferred stimulus (middle), and during delay activity following presentation of a nonpreferred stimulus (bottom). The dotted line indicates the value of excitatory synaptic currents needed to reach the (deterministic) firing threshold. In the two lower panels, the dotted boxes indicate the value of the corresponding component during spontaneous activity, to show the differences between delay and spontaneous activity. Background external inputs are superthreshold. Recurrent circuit is dominated by inhibition (brown) over excitation (orange) in the spontaneous state, so that the net recurrent synaptic current is hyperpolarizing (blue). During delay activity both recurrent excitation and inhibition are larger and dynamically balance each other, in such a way that the overall synaptic excitation becomes slightly larger following a preferred stimulus (leading to persistent activity at an elevated rate) than after a nonpreferred stimulus.

Figure 4.5 Gamma oscillations during working memory. (A) Spatiotemporal firing pattern of a spatial working memory model same as in Figure 4.2 (with slightly different parameters) except that firing rates are color-coded. (B) 500 ms blowup of (A) to show synchronous oscillations in the spatiotemporal activity pattern (top), the local field potential (middle) and membrane potential of a single neuron (bottom). On the right is shown the power spectrum of the local field, demonstrating a large peak at about 40 Hz. (Adopted from Compte *et al.* [2000] with permission.)

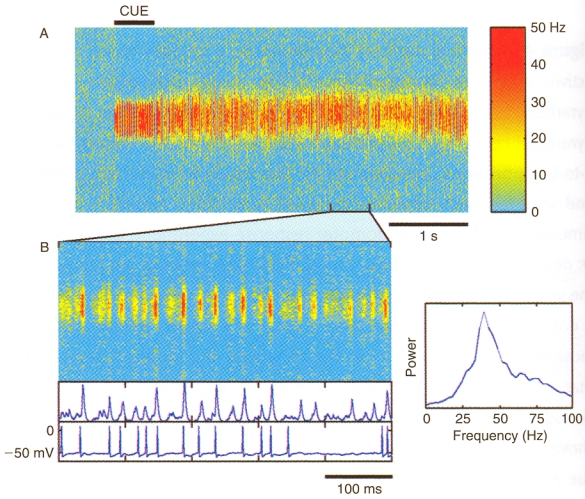


Figure 4.7 A spatial working memory model, with single neurons endowed with three compartments (soma, proximate and distal dendrites) and a number of voltage-gated ion channels. (A) Left: schematic single pyramidal cell model; right: spatiotemporal network activity (top) and membrane potential of a single cell (bottom) in a simulation of the delayed oculomotor experiment. Data provided by J. Tegnér (2002). (B) Electroresponsiveness of an isolated pyramidal cell model with a nonselective cation current ICan. The calcium-dependent activation of ICan is slow, leading to a ramping-up time course of the neural response. A few action potentials are still fired after stimulus extinction, in parallel with a slow deactivation of ICan. Notice that the neuron is not bistable; it returns to stable resting state. (C) Slow ionic currents (here ICan) reduce the minimum level of NMDAR that is required for sustained delay activity. Further increase in gCan renders the neuron intrinsically bistable (not shown). (Adopted from Tegnér *et al.* [2002] with permission.)

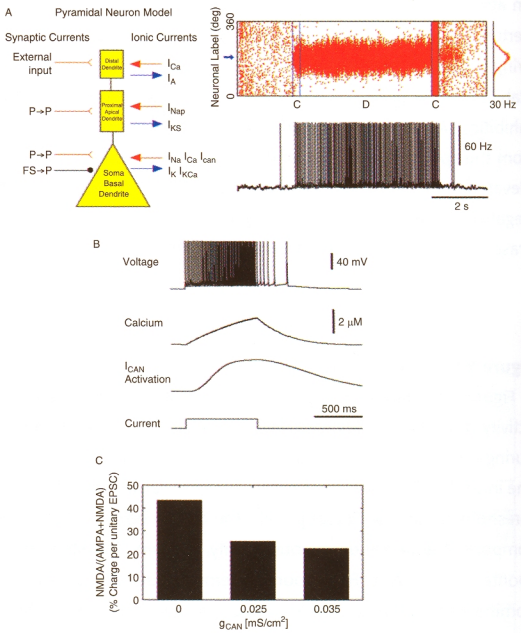


Figure 4.8 Resistance against distractors. (A) In the spatial working memory model, the initial cue (upper arrow on the left) triggers persistent activity centered at 180°. During the delay, a second cue (distractor) is shown briefly (lower arrow on the left). When the distractor is close to the initial stimulus, the network performs a vector sum so that the final remembered cue is half-way between the two (arrow on the right). On the other hand, when the distractor is far away from the initial stimulus, the network operates in a winner-take-all regime, so that the final remembered cue is either the initial stimulus or the distractor, depending on the strength of the stimuli. (B) Behavior of an object working memory model as function of dopamine modulation of NMDAR-mediated recurrent excitation and $GABA_AR$ inhibition (x-axis) and amplitude of cue stimulation (y-axis). A very weak stimulus (initial cue) cannot elicit persistent activity (lower left region), whereas a powerful stimulus (distractor) can override recurrent dynamics and disrupt delay activity (upper left region). The desirable behavior (robust persistent activity in spite of distractors) (middle right region) is sensitive to dopamine modulations. (Adopted from Brunel & Wang [2001] with permission.)

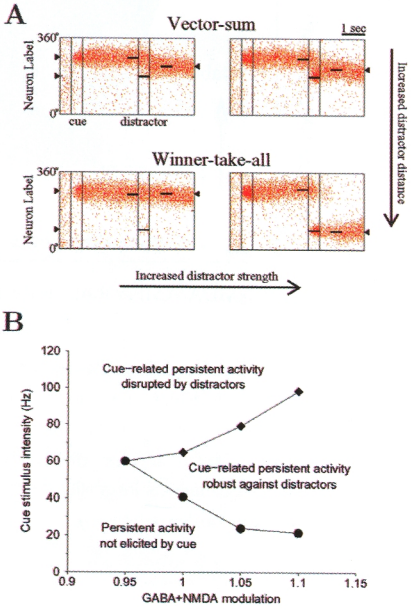
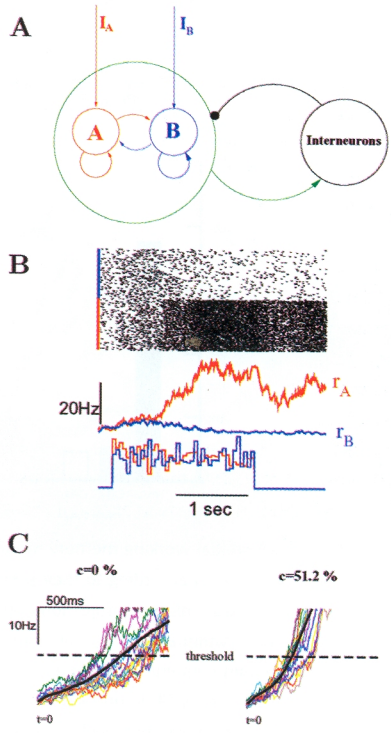


Figure 4.9 (A) A simple model for two-alternative forced-choice tasks. There are two pyramidal cell groups, each of which is selective to one of the two directions (A=left, B=right) of random moving dots in a visual motion discrimination experiment. Within each pyramidal neural group there are strong recurrent excitatory connections which can sustain persistent activity triggered by a transient preferred stimulus. The two neural groups compete through feedback inhibition from interneurons. The motion coherence is expressed as $c = (\mu A - \mu B)/(\mu A + \mu B)$, where μA and μB are the mean values of inputs IA and IB. (B) A network simulation with zero coherence. Top to bottom: network spiking raster, population firing rates rA and rB, stochastic inputs IA and IB. Note the initial slow ramping (time integration) and eventual divergence of rA and rB (categorical choice). (C) In reaction time simulations, when one of the two neural groups reaches a fixed threshold (15 Hz) of population firing activity, the decision is made and the deliberation or decision time is read out. The decision time is longer and more variable at low coherence (left) than at high coherence (right). (Adopted from Wang [2002] with permission.)



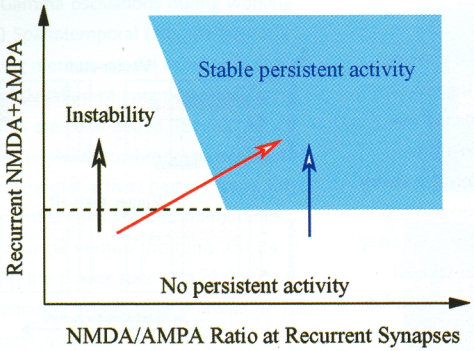


Figure 4.11 Schematic depiction of the dependence of stable persistent activity on both sufficiently strong recurrency (y-axis) and large NMDA/AMPA ratio at local excitatory synapses (x-axis). A circuit that does not exhibit persistent activity may be endowed with this ability by strengthening excitatory connections while preserving a relatively large NMDA/AMPA ratio (blue arrow). However, an enhancement of recurrency at a low NMDA/AMPA ratio can lead to network dynamical instability (black arrow), in which case the NMDA/AMPA ratio needs to be increased simultaneously (red arrow).

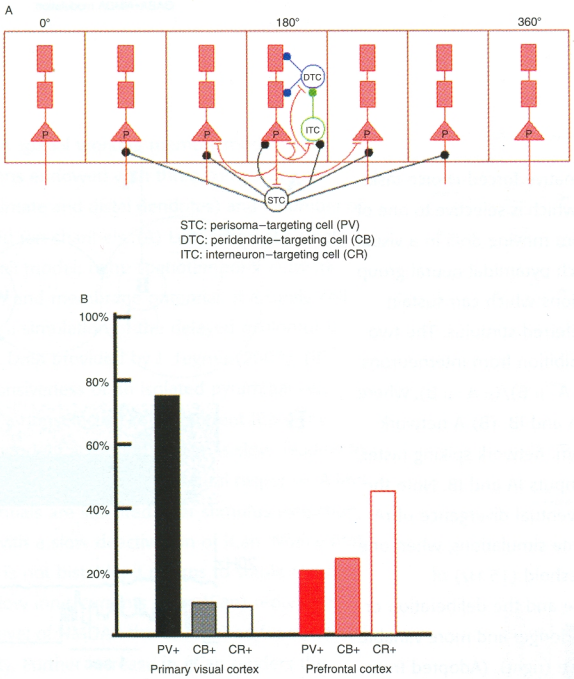


Figure 4.13 (A) A spatial working memory model with three subclasses of GABAergic interneurons. Pyramidal (P) neurons are arranged according to their preferred cues (0 – 360°). There are localized recurrent excitatory connections, and broad inhibitory projections from perisoma-targeting (parvalbumin-containing, PV) fast-spiking neurons to P cells. Within a column, calbindin-containing (CB) interneurons target the dendrites of P neurons, whereas calretinin-containing (CR) interneurons preferentially project to CB cells. Excitation of a group of pyramidal cells recruits locally CR neurons, which sends enhanced inhibition to CB neurons, leading to dendritic disinhibition of the same pyramidal cells. (Adopted from Wang *et al.* [2004] with permission.) (B) Proportional distribution of PV, CB and CR expressing GABAergic cells in primary visual cortex and prefrontal cortex. See text for details.