Chapter

14 Attractor Network Dynamics, Transmitters, and Memory and Cognitive Changes in Aging

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1 Introduction

This chapter starts with a concise overview of attractor networks that are implemented in the cerebral cortex by excitatory connections between pyramidal cells, and that implement processes such as short-term memory, episodic memory, attention, and decision-making. Then, the means by which the decline of some neurotransmitters that occurs with aging influence the stability of these attractor networks are described, with this analysis having implications for treatment.

An *attractor* network is a group of neurons with excitatory interconnections that can settle into a stable pattern of firing [1–4] (see Chapter 8 for a simple conceptual introduction to attractor networks). This chapter explains how attractor networks in the cerebral cortex are important for long-term memory, short-term (working) memory, attention, and decision-making, with a fuller description as well as demonstration programs that run in Matlab or Octave provided [1]. The chapter then describes how the random firing of neurons can influence the stability of these networks by introducing stochastic noise, and how these effects are involved in probabilistic decision-making and are also implicated in some disorders of cortical function, such as poor short-term memory and attention that occur with during normal aging [5]. Each memory pattern stored in an attractor network through associative synaptic modification consists of a subset of the neurons firing. These patterns could correspond to short-term memories, long-term memories, perceptual representations, or thoughts.

2 Attractor Networks

2.1 Attractor Network Architecture, and the Storage of Memories

2.1.1 Architecture and Memory Storage

The architecture of an attractor or autoassociation network is shown in Figure 14.1. External inputs e_i activate the neurons in the network, and produce firing y_i, where i refers to the ith neuron. The neurons are connected by recurrent collateral synapses w_{ij}, where j refers to the jth synapse on a neuron. By these synapses, an input pattern on e_i is associated with itself, and thus the network is referred to as an autoassociation network [6–8]. Because there is positive feedback via the recurrent collateral excitatory synaptic connections, the network can sustain persistent firing. These synaptic connections are assumed to build up by an associative (Hebbian) learning mechanism [9] (according to which, the more two neurons are simultaneously active, the stronger the neural connection becomes). The associative learning rule for the change in the synaptic weight is as shown in Eqn. (1):

$$\delta w_{ij} = k \cdot y_i \cdot y_j \tag{1}$$

where k is a constant, y_i is the activation of the dendrite (the postsynaptic term), y_j is the presynaptic firing rate, and δw_{ij} is the synaptic weight. The inhibitory interneurons are not shown. The inhibitory interneurons receive inputs from the pyramidal cells and make negative feedback connections onto the pyramidal cells to control their activity.

In order for biologically plausible autoassociative networks to store information efficiently, heterosynaptic long-term depression (LTD) (as well as long-term potentiation) is required [1, 8, 10]. This type of LTD helps to remove the correlations between the training patterns that arise when the neurons have positive-only firing rates. The effect of the LTD can be to enable the effect of the mean presynaptic firing rate to be subtracted from the training patterns [1, 8, 10].

2.1.2 Memory Recall

During recall, the external input e_i is applied and produces output firing, operating through the nonlinear activation function described below. The firing is fed back by the recurrent collateral axons shown in

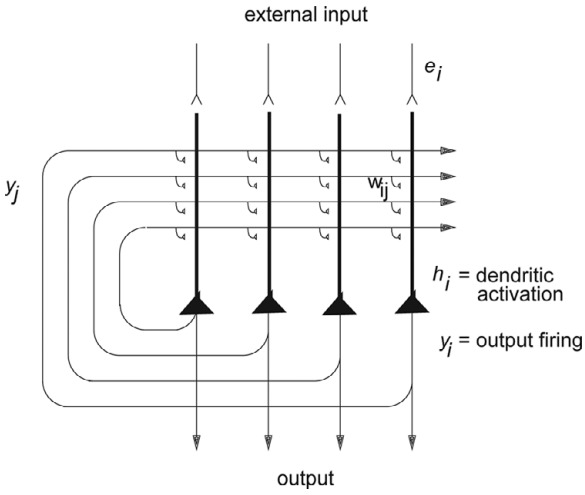

Figure 14.1 The architecture of an autoassociative or attractor neural network (see text).

Figure 14.1 to produce activation of each output neuron through the modified synapses on each output neuron. The activation h_i produced by the recurrent collateral effect on the ith neuron is the sum of the activations produced in proportion to the firing rate of each axon y_j operating through each modified synapse w_{ij}, that is,

$$h_i = \Sigma_j y_j w_{ij} \tag{2}$$

where Σ_j indicates that the sum is over the C input axons to each neuron, indexed by j. This is a dot or inner product computation between the input firing vector y_j (j = 1, C) and the synaptic weight vector w_{ij} (j = 1, C) on neuron i. It is because this is a vector similarity operation, closely related to a correlation between the input vector and the synaptic weight vector, that many of the properties of attractor networks arise, including completion of a memory when only a partial retrieval cue is applied (often referred to as content addressable memory) [1]. The output firing y_i is a nonlinear function of the activation produced by the recurrent collateral effect (internal recall) and by the external input e_i:

$$y_i = f(h_i + e_i) \tag{3}$$

The activation function should be nonlinear, and may be, for example, binary threshold, linear threshold, sigmoid, and so on. The threshold at which the activation function operates is set in part by the effect of the inhibitory neurons in the network (not shown in Figure 14.1). The threshold prevents the positive feedback inherent in the operation of attractor networks from leading to runaway neuronal firing. It also allows optimal retrieval of a memory without interference from other memories stored in the synaptic weights [1, 3].

The recall state (which could be used to implement short-term memory, or memory recall) in an attractor network can be thought of as a local minimum in an energy landscape [2], where the energy would be defined as:

$$E = -\frac{1}{2}\sum_{i,j} w_{ij}\left(y_i - \langle y \rangle\right)\left(y_j - \langle y \rangle\right) \tag{4}$$

where y_i is the firing of neuron i, and $\langle y \rangle$ indicates the average firing rate. The intuition here is that, if both y_i and y_j are above their average rates and are exciting each other through a strong synapse, then the firing will tend to be stable and maintained, resulting in a low energy state that is stable. Although this energy analysis applies formally only with a fully connected network with symmetric synaptic strengths between neurons (which would be produced by an associative learning rule), it has been shown that the same general properties apply if the connectivity is diluted and becomes asymmetric [7, 8, 11–13].

Autoassociation attractor systems have two types of stable fixed points: a spontaneous state with a low firing rate, and one or more persistent states with high firing rates in which the neurons keep firing (Figure 14.2). Each one of the high firing rate attractor states can implement a different memory. When the system is moved to a position in the space by an external retrieval cue stimulus, it will move to the closest stable attractor state. The area in the space within which the system will move to a stable attractor state is called its basin of attraction. This is the process involved in completion of a whole memory from a partial retrieval cue.

2.2 Properties of Attractor Networks

2.2.1 Completion

An important and useful property of these attractor networks is that they complete an incomplete input vector, allowing recall of a whole memory from a small fraction of it. The memory recalled in response to a fragment is that stored in the memory that is closest in pattern similarity (as measured by the dot product, or correlation). Because the recall is iterative and progressive, the recall can be perfect.

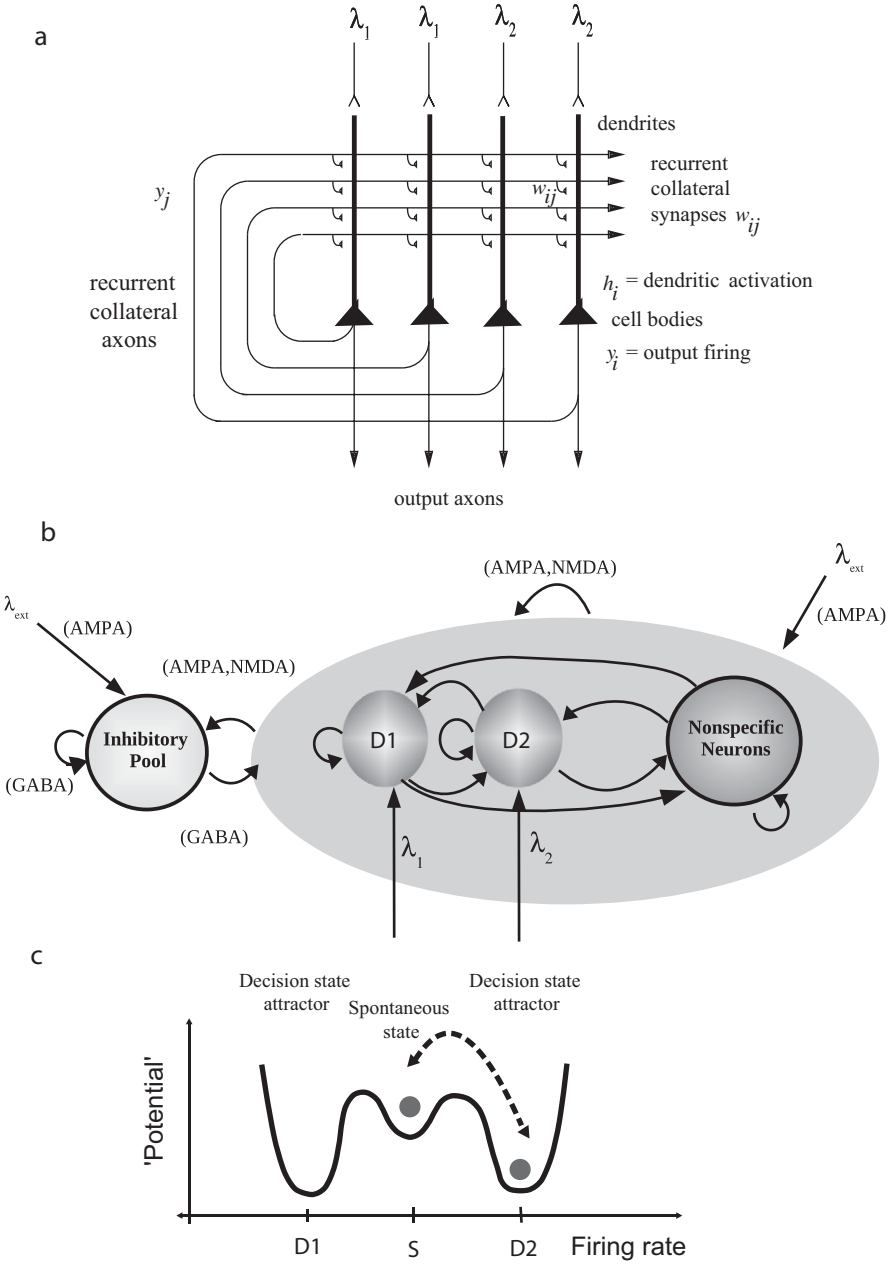

Figure 14.2 (a) Attractor or autoassociation network architecture for decision-making. The evidence for decision 1 is applied via the λ_1 inputs, and for decision 2 via the λ_2 inputs. The synaptic weights *wij* have been associatively modified during training in the presence of λ_1 and at a different time of λ_2. When λ_1 and λ_2 are applied, each attractor competes through the inhibitory interneurons (not shown) until one wins the competition and the network falls into one of the high firing rate attractors that represents the decision. The noise in the network caused by the random spiking of the neurons means that on some trials, for given inputs, the neurons in the decision 1 attractor are more likely to win, and on other trials the neurons in the decision 2 attractor are more likely to win. This makes the decision-making probabilistic, for, as shown in (c), the noise influences when the system will jump out of the spontaneous firing stable (low-energy) state S, and whether it jumps into the high firing state for decision 1 or decision 2 (D). (b) The architecture of the integrate-and-fire network used to model vibrotactile decision-making (see text).

2.2.2 Short-Term Memory

An autoassociation or attractor memory not only is useful as a long-term memory, in, for example, the memory for particular past episodes (see below), but can also be used as a short-term (working) memory, in which iterative processing around the recurrent collateral loop keeps a representation or series of representations active until another input cue is received or the task is completed. This is often used by the brain and is a prototypical property of cerebral neocortex [1].

2.2.3 Graceful Degradation or Fault Tolerance

If the synaptic weight vector $\mathbf{w}_i$ on each neuron has synapses missing (e.g., during development) or loses synapses (e.g., with brain damage or aging), then the activation h_i will still be reasonable, because h_i is the dot product (correlation) of the input firing rate vector and the weight vector. The same argument applies if whole input axons are lost. If an output neuron is lost, then the network cannot itself compensate for this, but the next network in the brain is likely to be able to generalize or complete if its input vector has some elements missing, as would be the case if some output neurons of a preceding autoassociation network were damaged. These processes constitute graceful degradation.

2.2.4 Storage Capacity, and the Sparseness of the Representation

Hopfield, using the approach of statistical mechanics, showed that, in a fully connected attractor network with fully distributed binary representations (e.g., for any one pattern, half the neurons are in the high firing state of 1, and the other half are in the low firing state of 0 or −1), the number of stable attractor states, corresponding to the number of memories that can be successfully retrieved, is approximately $0.14C$, where C is the number of connections on each neuron from the recurrent collateral connections [2–4].

We (Treves and Rolls) have performed quantitative analyses of the storage and retrieval processes in attractor networks [1, 7, 8, 11, 12]. We have extended previous formal models of autoassociative memory (see [3]) by analyzing a network either with graded response units (so as to represent more realistically the continuously variable rates at which neurons fire) or with incomplete connectivity [8, 11]. We have found that, in general, the maximum number, $p_{\max}$, of firing patterns that can be (individually) retrieved is proportional to the number C^{RC} of (associatively) modifiable recurrent collateral synapses per neuron, by a factor that increases roughly with the inverse of the sparseness, a, of the neuronal representation (see below for definition of sparseness).[1]

The outcome of these analyses is that the number of memories that can be stored in a cortical attractor network is proportional to the number of synapses per neuron and that, with the sparsenesses of the representations present in the cerebral cortex, the number of memories is on the order of the number of synapses per neuron. Thus, if a typical pyramidal neuron in the cerebral cortex has 10,000 synapses devoted to the recurrent collateral connections, then such a local network in a small part of the neocortex, perhaps 2 millimeters in radius, could play a role in storing on the order of 10,000 memories [1]. Some details follow.

The neuronal population sparseness a of the representation can be measured by extending the binary notion of the proportion of neurons that are firing to any one stimulus or event as

$$a = \left(\sum_{i=1,n} r_i/N\right)^2 / \sum_{i=1,n} \left(r_i^2/N\right) \tag{5}$$

where r_i is the firing rate of the ith neuron in the set of N neurons. The sparseness ranges from $1/N$, when only one of the neurons responds to a particular stimulus (a local or grandmother cell representation), to a value of 1.0, attained when all the neurons are responding to a given stimulus. Approximately,

$$p_{\max} \cong \frac{C^{RC}}{a \ln (1/a)} k \tag{6}$$

where k is a factor that depends weakly on the detailed structure of the rate distribution, on the connectivity pattern, and so on, but is roughly in the order of 0.2–0.3 [8]. For example, for $C^{RC} = 12{,}000$ (the number of recurrent collateral synapses on a hippocampal CA3 neuron in the rat [14]) and $a = 0.02$, $p_{\max}$ is calculated to be approximately 36,000. This analysis emphasizes the utility of having a sparse representation in the

[1] Each memory representation is precisely defined in the theory: it is a set of firing rates of the population of neurons (which represent a memory) that can be stored and later retrieved, with retrieval being possible from a fraction of the originally stored set of neuronal firing rates.

hippocampus, for this enables many different memories to be stored [1, 15, 16]. These quantitative analyses have been confirmed numerically [1, 13, 17].

2.2.5 The Dynamics of the Recurrent Attractor Network – Fast Recall

The analysis of the capacity of a recurrent network described above considered steady state conditions of the firing rates of the neurons. The question arises of how quickly the recurrent network would settle into its final state. If these settling processes took on the order of hundreds of milliseconds, they would be much too slow to contribute usefully to cortical activity, whether in the hippocampus or the neocortex [1, 18–20].

It has been shown that if the neurons are treated not as McCulloch–Pitts neurons, which are simply "updated" at each iteration or cycle of time steps (and assume the active state if the threshold is exceeded), but instead are analyzed and modeled as "integrate-and-fire" neurons in real continuous time, then the network can effectively "relax" into its recall state very rapidly, in one or two time constants of the synapses [1, 7, 21, 22]. This corresponds to perhaps 20 milliseconds in the brain. One factor in this rapid dynamics of autoassociative networks with brain-like integrate-and-fire membranes and synaptic properties is that, with some spontaneous activity, some of the neurons in the network are close to firing threshold already before the recall cue is applied, and hence some of the neurons are very quickly pushed by the recall cue into firing. Thus, information starts to be exchanged very rapidly (within 1–2 milliseconds of brain time) through the modified synapses by the neurons in the network. The progressive exchange of information, starting early on within what would otherwise be thought of as an iteration period (of perhaps 20 milliseconds, corresponding to a neuronal firing rate of 50 spikes per second), is the mechanism accounting for rapid recall in an autoassociative neuronal network made biologically realistic in this way. Further analysis of the fast dynamics of these networks, if they are implemented in a biologically plausible way with integrate-and-fire neurons, is provided in appendix A5 of Rolls and Treves [7], and elsewhere [1, 20–22].

2.3 Attractor Networks for Short-Term Memory

Pyramidal neurons in the cerebral cortex have a relatively high density of excitatory connections to each other within a local area of 1–3 millimeters [1, 23–25]. These local recurrent collateral excitatory connections provide a positive-feedback mechanism (which is kept under control by GABA inhibitory interneurons) that enables a set of neurons to maintain their activity for many seconds to implement a short-term memory [26]. Each memory is formed by the set of the neurons in the local cortical network that were coactive when the memory was formed, resulting in strengthened excitatory connections between that set of neurons through the process of long-term potentiation, which is a property of these recurrent collateral connections.

Attractor networks appear to operate in many cortical areas, including the prefrontal cortex, an area that is important in attention and short-term memory, as shown, for example, by firing in the delay period of a short-term memory task [1, 27–32]. Short-term memory is the ability to hold information online during a short time period [32].

It has been proposed that, whereas it is a property of all cortical areas that they have an ability to maintain neuronal activity by the attractor properties implemented by the recurrent collateral connections, the prefrontal cortex has a special role in short-term memory because it can act as an offline store as follows [1]. First, we note that a perceptual brain area, such as the inferior temporal cortex, must respond to every new incoming set of objects in the world so that we can see them, and this is inconsistent with maintaining their firing in an attractor state that represents an object or objects seen seconds ago. For this reason, for a short-term memory to be maintained during periods in which new stimuli are to be perceived, there must be separate networks for the perceptual and short-term memory functions, and indeed two coupled networks, one in the inferior temporal visual cortex for perceptual functions, and another in the prefrontal cortex for maintaining the short-term memory, for example, when intervening stimuli are being shown, provide a precise model of the interaction of perceptual and short-term memory systems [33, 34]. This model shows how a prefrontal cortex attractor (autoassociation) network could be triggered by a sample visual stimulus represented in the inferior temporal visual cortex in a delayed match to sample task, and could keep this attractor active during a memory interval in which intervening stimuli are shown. Then, when the sample stimulus reappears in the task as a match stimulus, the inferior temporal

cortex module shows a large response to the match stimulus because it is activated by both the visual incoming match stimulus and the consistent back-projected memory of the sample stimulus still being represented in the prefrontal cortex memory module. The prefrontal attractor can be stimulated into activity by the first stimulus when it is inactive, but once in its high firing rate attractor state, it is relatively stable because of the internal positive feedback, and is not likely to be disturbed by further incoming stimuli. The internal recurrent connections must be stronger than the feedforward and feedback connections between the two cortical areas for this to work [1, 33, 34].

This computational model makes it clear that in order for ongoing perception to occur unhindered, implemented by posterior cortex (parietal and temporal lobe) networks, there must be a separate set of modules that is capable of maintaining a representation over intervening stimuli. This is the fundamental understanding offered for the evolution and functions of the dorsolateral prefrontal cortex, and it is this ability to provide multiple separate short-term attractor memories that provides, I suggest, the basis for its functions in planning [1].

The impairments of attention induced by prefrontal cortex damage may be accounted for in large part by an impairment in the ability to stably hold the object of attention in the short-term memory systems in the prefrontal cortex [1, 27, 35].

2.4 Stability of Attractor States

Using an integrate-and-fire approach, the individual neurons, synapses, and ion channels that comprise an attractor network can be simulated, and when a threshold is reached, the cell fires [1]. The firing times of the neurons can be approximately like those of neurons in the brain, approximately Poisson distributed; that is, the firing time is approximately random for a given mean rate. The random firing times of neurons are one source of noise in the attractor network and can influence the stability of the network [1, 36–39]. The attractor dynamics can be pictured as energy landscapes in which basins of attraction correspond to valleys and the attractor states to fixed points at the bottom of the valleys. The stability of an attractor is characterized by the average time in which the system stays in the basin of attraction under the influence of noise, which provokes transitions to other attractor states. Noise results from the interplay between the Poissonian character of the spikes and the finite-size effect due to the limited numbers of neurons in the network. Two factors determine the stability. First, if the attractors are shallow (as in the left compared with the right valley in Figure 14.2c), less force is needed to move to a neighboring valley. *If the firing rates of the neurons are low, this reduces the depth of the basins of attraction by reducing the positive feedback between the set of neurons in the attractor. This is a key concept in understanding the effects of aging on memory, attention, and cognition, and a key foundation for many of the hypotheses about the effects of normal aging that are considered later in this chapter.* Second, a high level of noise increases the likelihood that the system will jump over an energy boundary from one state to another. We envision that the brain, as a dynamical system, has characteristics of such an attractor system, replete with statistical fluctuations.

This type of model can then be applied to the prefrontal cortex and used to link these low-level neuronal properties to the cognitive functions such as short-term memories that result from the interactions between thousands of neurons in the whole network. In order to maintain a short-term memory, these interactions have to remain stable, and several factors influence the stability of such a short-term memory attractor state with noise inherent in its operation.

First, the stable states of the network are the "low energy" states in which one set of the neurons, connected by strengthened recurrent collateral synapses, and representing one memory, is activated (see Figure 14.2). The higher the firing rates of this set of neurons, the stronger will be the negative feedback inhibition by the GABA inhibitory interneurons to the other excitatory (pyramidal) neurons in the network. This will keep the short-term memory state stable and will prevent distracting inputs to the other, inhibited neurons in the network from taking over [40]. Any factor that reduces the currents through the NMDA receptor channels (NMDARs) on the pyramidal cells (or via AMPA receptors) would decrease the firing rates of the set of activated neurons and tend to make the network more distractible [41–43].

Second, the strong synaptic connections implemented by the recurrent collateral synapses between the excitatory neurons in the network (e.g., the pyramidal cells in the prefrontal cortex) also tend to

promote stability by enhancing the firing of the neurons that are active for a short-term memory [44]. This helps to keep the energy low in the Hopfield equation (see Eqn. 4), and thus to make it difficult to jump from one energy minimum over a barrier to a different energy minimum that represents a different memory.

Third, the operation of the network is inherently noisy and probabilistic, owing to the random spiking of the individual neurons in the network and the finite size of the network [45–49]. The random spiking will sometimes (i.e., probabilistically) be large in neurons that are not among those in the currently active set representing the short-term memory in mind; this chance effect, perhaps in the presence of a distracting stimulus, might make the network jump over an energy barrier between the memory states into what becomes a different short-term memory, resulting in distraction. In a different scenario, the same type of stochastic noise could make the network jump from a spontaneous state of firing, in which there is no item in short-term memory, to an active state in which one of the short-term memories becomes active. The effects of noise operating in this way would be more evident if the firing rates were low (resulting in a low energy barrier over which to jump) or if the GABA inhibition was reduced, which would make the spontaneous firing state less stable. GABA interneurons normally inhibit the neurons that are not in the active set that represent a memory, but hypofunction of the NMDARs on GABA interneurons could diminish this inhibition.

Fourth, the stability of the attractor state is enhanced by the long time constants (around 100 milliseconds) of the NMDARs in the network [50–53]. The contribution of these long time constants (long in relation to those of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) excitatory receptors, which are on the order of 5–10 milliseconds) is to smooth out in time the statistical fluctuations that are caused by the random spiking of populations of neurons in the network, and thus to make the network more stable and less likely to jump to a different state. The different state might represent a different short-term memory, or the noise might return the active state back to the spontaneous level of firing, producing failure of the short-term memory and failure to maintain attention. Further, once a neuron is strongly depolarized, the voltage dependence of the NMDARs may tend to promote further firing [50]. If the NMDARs were less efficacious, the short-term memory network would be less stable because the effective time constant of the whole network would be reduced, owing to the greater relative contribution of the short time constant AMPA receptors to the effects implemented through the recurrent collateral excitatory connections between the pyramidal cells [51, 52, 54].

2.5 Attractor Network Stability and Psychiatric Disorders

It is hypothesized that some of the cognitive symptoms of schizophrenia, including poor short-term memory and attention, can be related to a reduced depth in the basins of attraction of the attractor networks in the prefrontal cortex that implement these functions [42, 43, 55]. The reduced depth of the basins of attraction may be related to hypoglutamatergia [56, 57] and/or changes in dopaminergic function, which act partly by influencing glutamatergic function [1, 43, 58–61]. The negative and positive symptoms of schizophrenia may be related to similar underlying changes, but expressed in different parts of the brain, such as the orbitofrontal and anterior cingulate cortex, as well as the temporal lobes [1, 42, 43, 55].

Obsessive-compulsive disorder has been linked to overstability in cortical attractor networks involved in short-term memory, attention, and action selection. It is hypothesized, at least in part, to be induced by hyperglutamatergia [1, 44].

In depression, the theory is being developed that the lateral orbitofrontal cortex, which is involved in detecting when rewards are smaller than expected, has a non-reward attractor that is overactive, resulting in persistent negative ruminating thoughts, hence sadness [62–66].

2.6 Attractor Networks, Noise, and Decision-making

A biologically plausible model, motivated and constrained by neurophysiological data, has been formulated to establish an explicit link between probabilistic decision-making and the way in which the noisy (i.e., stochastic) firing of neurons influences which attractor state (representing a decision) is reached when there are two or more competing inputs or sources of evidence to the attractor network [1, 38,

39, 48, 67–71]. The way in which these decision-making attractor network models operate is as follows. The model is an attractor network set up to have two (or more) possible high firing rate attractor states, one for each of the two (or more) decisions, as illustrated in Figure 14.2b. The evidence for each decision (1 vs. 2, etc.) biases each of the two attractors via the external inputs λ_1 and λ_2. The attractors are supported by strengthened synaptic connections in the recurrent collateral synapses between the (e.g., cortical pyramidal) neurons activated when λ_1 is applied, or when λ_2 is applied. (This is an associative or Hebbian process set up during a learning stage by a process like long-term potentiation.) When inputs λ_1 and λ_2 are applied, there is positive feedback via the recurrent collateral synaptic connections and competition is implemented through the inhibitory interneurons so that there can be only one winner. The network starts in a low spontaneous state of firing. When λ_1 and λ_2 are applied, there is competition between the two attractors, each of which is pushed toward a high firing rate state, and eventually, depending on the relative strength of the two inputs and the noise in the network caused by the random firing times of the neurons, one of the attractors will win the competition, and it will reach a high firing rate state. The firing of the neurons in the other attractor will be inhibited, resulting in a low firing rate. Because this is a nonlinear positive feedback system, the final firing rates are in what is effectively a binary decision state of high firing rate or low firing rate and do not reflect the exact relative values of the two inputs, λ_1 and λ_2, once the decision is reached. The noise in the network, caused by the random spiking of the neurons, is important to the operation of the network because it enables the network to jump out of a stable spontaneous rate of firing to a high firing rate and to do so probabilistically, depending on whether, on a particular trial, there is relatively more random firing in the neurons of one attractor than the other. This can be understood in terms of energy landscapes, where each attractor (the spontaneous state, and the two high firing rate attractors) is a low energy basin, and the spiking noise helps the system to jump over an energy barrier into another energy minimum, as illustrated in Figure 14.2c. If λ_1 and λ_2 are equal, then the decision that is taken is random and probabilistic, with the noise in each attractor determining which decision is taken on a particular trial. If one of the inputs is larger than the other, then the decision is biased toward it, but is still probabilistic. Because this is an attractor network, it has short-term memory properties implemented by the recurrent collaterals, which tend to promote a state once it is started. These help it to maintain the firing once it has reached the decision state, enabling a suitable action to be implemented even if this takes some time.

It might be posited that, if the depth of the basins of attraction is impaired with normal aging by one of more of the mechanisms described below, then this impairment might have an effect on decision-making systems of this type in the brain. It is possible in these circumstances that decisions might become noisier, that is, less closely related to the decision variables; slower; and not maintained as well in the short term. Planning related to the decision would not be maintained as persistently as with unreduced depths of the basins of attraction. This is an idea that arises from considering this type of decision-making system, and it would be of interest to further explore this proposal.

2.7 Hippocampal versus Neocortical Attractor Networks

The neocortical networks have local recurrent collateral connections between the pyramidal cells that achieve a high density only for a few millimeters across the cortex. It is hypothesized that this organization enables the neocortex to have many local attractor networks, each concerned with a different type of processing, short-term memory, long-term memory, and decision-making [1]. This is important, for recall that the capacity of an attractor network is set to first order by the number of connections onto a neuron from other neurons in the network. If there were widespread recurrent collateral connections in the neocortex so that the whole neocortex operated as a single attractor, the total memory capacity of the neocortex would be only that of a single attractor network (on the order of thousands of memories), a possibility that has been ruled out [1, 72]. There are great advantages in having large numbers of local but weakly coupled neocortical attractor networks. Some have been described above and many more are described by Rolls [1, 73].

It has been suggested, however, that one network in the brain, the hippocampal CA3 network, does operate as a *single* attractor network [1, 7, 15, 16, 74–83] (see related approaches, not emphasizing the

relative importance of a single attractor network (or CA3 [84]), including [85–88])). Part of the anatomical basis for this single attractor network is that the recurrent collateral connections between the CA3 neurons are very widespread and have a chance of contacting any other CA3 neuron in the network [14, 89, 90]. The underlying theory is that the widespread connectivity in this network allows any one set of active neurons, perhaps representing one part of an episodic memory, to have a fair chance of making modifiable synaptic contacts with any other set of CA3 neurons, perhaps representing another part of an episodic memory. (An episodic memory is a memory of a single event or episode, such as where one ate dinner, with whom one ate, what was eaten, and what was discussed.) This widespread connectivity providing for a single attractor network means that any one part of an episodic memory can be associated with other components of events in the episodic memory. (This is what I mean by calling this an arbitrary memory, in that any arbitrary set of events can be associated with any other.) This functionality would be impossible in the neocortex, as the connections are local. Thus, this is a special contribution that the hippocampus can make when encoding an event in episodic memory [1, 81, 91, 92]. Any reduction of the firing rates of neurons in this CA3 network and the hippocampal system in general, which might occur with normal aging, would be expected to impair episodic memory by reducing the depths of the basins of attraction of hippocampal memory-related networks.

3 Attractor Networks, Transmitters, and Normal Aging

3.1 Introduction

As described above, cognitive symptoms such as poor short-term (working) memory and a decrement in top-down attention could arise from reduced depth in the basins of attraction of prefrontal and other cortical networks, as well as the effects of noise [1, 5, 39]. The hypothesis is that the reduced depth in the basins of attraction would make short-term memory unstable, so that sometimes the continuing firing of neurons that implement short-term memory would cease, and the system, under the influence of noise, would fall back out of the short-term memory state into spontaneous firing. Top-down attention requires an intact short-term memory to hold the object of attention in mind. This is the source of the top-down attentional bias that influences competition from other networks that are receiving incoming signals. Therefore, disruption of short-term memory is also predicted to impair the stability of attention, as well as many other cognitive and executive functions that depend on the stability of short-term memory.

In this section I consider the hypothesis that the impairments in short-term memory and attention that are commonly associated with normal aging occur because the stochasticity of the dynamics is increased. This increase is caused by a reduced depth in the basins of attraction of cortical attractor networks involved in short-term memory and attention. Reduced short-term memory and impaired attention are commonly associated with aging, as are impairments in episodic memory [93]. Short-term memory and top-down attention are related to the operation of the dorsolateral prefrontal cortex [94, 95] using attractor networks that also provide the source of the top-down bias for attention [1]. Episodic memory utilizes attractor networks in the hippocampus [1, 16]. First, we examine some of the neurobiological changes that occur during normal aging and formulate hypotheses about how they might alter the depth of the basins of attraction of the attractor networks in the brain involved in short-term memory, attention, and episodic memory. Then we test these hypotheses by integrate-and-fire simulations with stochastic dynamics (caused by the almost Poisson nature of the spike trains of the neurons) in order to investigate how these neurobiological changes may influence the performance of these memory and attention systems. This leads to a discussion of ways in which some of the effects found might be ameliorated by different types of treatment.

Given that there is much knowledge about the neurobiology of normal aging [96, 97], an aim of the present approach is to provide a mechanistic, computational neuroscientific, stochastic neurodynamics framework for analysis of how the operation of cortical memory circuits involved in short-term memory, attention, and episodic memory, are altered by these changes [5]. This in turn has implications for how to ameliorate the changes in the operation of cortical networks during normal aging.

Neurodynamical hypotheses about the effects of the neurobiology of aging on attractor network functions in memory, attention, and cognition are developed next.

3.2 NMDA Receptor Hypofunction

One change associated with aging is a decrease in the functions of the NMDA receptors [98]. This change would act to reduce the depth of the basins of attraction, both by reducing the firing rate of the neurons in the active attractor and by decreasing the strength of the potentiated synaptic connections that support each attractor as the currents passing through these potentiated synapses decrease. If the NMDA receptor–activated channel conductances are reduced, then the depth of the basins of attraction will be reduced because the firing rates decline as a result of reduced excitatory inputs to the neurons, and because the synaptic coupling weights are effectively reduced because the synapses can pass only reduced currents.

I, therefore, hypothesize that with normal aging, *short-term memory and attention* will be impaired because the basins of attraction of the prefrontal cortex attractor networks mediating these functions [95, 99] and of other postcentral cortex areas that send inputs to the prefrontal cortex will have reduced depth and will therefore be less stable. This loss of stability will result in an increased proportion of trials on which the short-term memory will not be maintained [1, 5, 73]. Similarly, I hypothesize that with aging, *episodic memory* will be impaired because the basins of attraction of the hippocampal attractor networks mediating these functions [1] will have a reduced depth and will therefore be less stable, resulting in an increased proportion of trials on which the episodic memory will not be correctly recalled and actively maintained for the short period when it is used. Reduced functionality of AMPA receptors might also contribute, though NMDA receptors are of especial interest because of their long time constants.

3.3 Dopamine

D1 receptor blockade in the prefrontal cortex can impair short-term memory [100, 101]. Part of the reason for this may be that D1 receptor blockade can decrease NMDA receptor–activated ion channel conductances [40, 58]. Thus part of the role of dopamine in the prefrontal cortex in short-term memory can be accounted for by a decreased depth in the basins of attraction of prefrontal attractor networks [43]. The decreased depth would be due to both the decreased firing rate of the neurons and the reduced efficacy of the modified synapses as their channels would be open less (see Eqn. 4). Dopaminergic innervation of the prefrontal cortex may decline with aging [102]. The decrease in dopamine could contribute to the reduced short-term memory and attention associated with aging, just as in Parkinson's disease, in which there are also be dopamine-related cognitive impairments.

During development, short-term memory and related executive functions implemented in the dorsolateral prefrontal cortex only mature when dopamine becomes functional in this cortical region [103]. These effects may also be related to an effect of dopamine acting, for example, via NMDA receptors [104] to increase neuronal firing rates and thus the stability of short-term memory attractor networks.

Tests of the neurodynamical hypothesis that reductions in dopamine in the prefrontal cortex in normal aging could, by reducing NMDA receptor–activated synaptic conductances, impair short-term memory and related attentional and executive functions are described in Section 3.7.1, "NMDA Receptor Hypofunction and Reduced Synaptic Strength."

3.4 Norepinephrine, cAMP, and HCN Channels

Norepinephrine (noradrenaline), acting on alpha2A-adrenoceptors, can strengthen working memory implemented in recurrent attractor neural networks in the dorsolateral prefrontal cortex by inhibiting cyclic adenosine monophosphate (cAMP) [105]. cAMP closes hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (see also Chapter 3). The HCN channels on the distal dendrites allow K^+ (and Na^+) to pass through, generating an h current that shunts the effects of synaptic inputs [106], including inputs from the recurrent collateral connections. Thus, noradrenaline, by reducing shunting inhibition of the synaptic inputs, strengthens the attractor network, that is, maintains it more stably for more prolonged periods. Part of the evidence comes from iontophoresis of agents that influence these cAMP-activated HCN channels on single neurons in the macaque dorsolateral prefrontal cortex [105].

Noradrenaline reaches the cortex from the locus coeruleus, and a reduction in noradrenaline in aging and mild cognitive impairment [107], together with a loss of alpha2A adrenoceptors in the aged prefrontal cortex [108] and decreased excitation of noradrenergic neurons [109], would thus tend to impair short-term

memory. The effect is modeled in the simulations described below, which involve decreasing the synaptic input associated with the recurrent collaterals by reducing the NMDA synaptic conductance. The effect is to reduce the firing rates of the excitatory (pyramidal) cells in the simulation and thus to make the short-term memory less stable by reducing the depth of the basins of attraction. The simulation described below in fact predicts the changes in the firing rates that have been found experimentally [105].

Although this may or may not be due only to changes in the noradrenergic system with aging, the loss of persistent firing is related to increased cAMP-K+ channel signaling [110] arising from a loss of phosphodiesterase-4A (PDE4A) [111]. The loss of PDE4A leads to hyperphosphorylation of tau and vulnerability to degeneration, an effect that is most relevant to Alzheimer's disease.

3.5 Impaired Synaptic Modification

Another factor that may contribute to the memory and cognitive changes associated with aging is that long-lasting associative synaptic modification, as assessed by long-term potentiation (LTP), is more difficult to achieve in older animals and decays more quickly [96] (see Chapter 3). This would tend to weaken the synaptic strengths that support an attractor, and this weakening could progress over time, thus directly reducing the depth of the attractor basins. This would impact episodic memory, the memory for particular past episodes, such as where one was at breakfast on a particular day, who was present, and what was eaten [1, 16, 83]. The reduction of synaptic strengths over time could also affect short-term memory, which requires that the synapses supporting a short-term memory attractor be modified in the first place using LTP, before the attractor is used [112].

In view of these changes, boosting glutamatergic transmission is being explored as a means of enhancing cognition and minimizing its decline in aging. Several classes of AMPA receptor potentiators have been described in the last decade. These molecules bind to allosteric sites on AMPA receptors, slow desensitization, and thereby enhance signaling through the receptors. Some AMPA receptor potentiating agents have been explored in rodent models [113]. These treatments might increase the depth of the basins of attraction.

Another factor is that Ca^{2+}-dependent processes affect Ca^{2+} signaling pathways and impair synaptic function in an aging-dependent manner, consistent with the Ca^{2+} hypothesis of brain aging and dementia [98] (see Chapter 3). In particular, an increase in Ca^{2+} conductance can occur in aged neurons. CA1 pyramidal cells in the aged hippocampus have an increased density of L-type Ca^{2+} channels that might lead to disruptions in Ca^{2+} homeostasis, contributing to the plasticity deficits that occur during aging [114].

My neurodynamical hypothesis is that with aging, impaired synaptic modification during learning and/or poorer maintenance of synaptic modifications after learning could impair episodic memory, short-term memory, and related attentional and executive functions. I test this below by analyzing the effects on the stochastic dynamics of attractor networks of reducing NMDA receptor–activated synaptic conductances to simulate the effect of less strong synapses.

3.6 Cholinergic Function

3.6.1 Cerebral Cortical Acetylcholine and Aging

Another change with aging is a reduction in cortical acetylcholine. Acetylcholine in the neocortex has its origin largely in the cholinergic neurons in the basal magnocellular forebrain nuclei of Meynert [115]. The correlation of clinical dementia ratings with the reductions in a number of cortical cholinergic markers such as choline acetyltransferase, muscarinic and nicotinic acetylcholine receptor binding, and levels of acetylcholine suggested an association between cholinergic hypofunction and cognitive deficits. This led to the formulation of the cholinergic hypothesis of memory dysfunction in senescence and in Alzheimer's disease [97]. In this section I generate hypotheses about how this reduction in acetylcholine in aging may influence the stochastic dynamics of attractor networks involved in short-term memory and thereby degrade cognitive functions that depend on short-term memory such as attention. For top-down attention, the subject to which attention is being allocated must be maintained in a short-term memory [73].

The cells in the basal magnocellular forebrain nuclei of Meynert lie just lateral to the lateral hypothalamus in the substantia innominata and extend forward through the preoptic area into the diagonal band of Broca [115]. The majority of these cells, but not all, are cholinergic [116], and they project directly

to the cerebral cortex [115]. They provide the major cholinergic input to the cerebral cortex. If they are lesioned, the cortex is depleted of acetylcholine [115]. Loss of these cells does occur in Alzheimer's disease, and there is consequently a reduction in cortical acetylcholine in this disease [97, 115]. This loss of cortical and hippocampal acetylcholine may contribute to episodic memory impairment as well as other cognitive impairments in patients with Alzheimer's disease; however, the cognitive impairment caused by a loss of these basal forebrain cholinergic neurons may not be either the earliest factor or the major factor in the pathogenesis of the cognitive impairments associated with Alzheimer's disease. In monkeys, it has been shown that damage to basal forebrain cholinergic neurons can also impair attention and short-term memory [116]. There are only limited numbers of these cholinergic basal forebrain neurons (on the order of thousands). Given that there is a relative paucity of these neurons, it is not likely that they are directly storing learned information because the number of different patterns that could be represented and stored is so small (the number of different patterns that could be stored is dependent in a leading way on the number of input connections to each neuron in a pattern associator [1]). With the projections of these few neurons distributed throughout the cerebral cortex, the memory capacity of the whole system would be impractically small. Instead, these neurons could modulate storage in the cortex of information derived from what provides the numerical majority of input to cortical neurons, the glutamatergic terminals of other cortical neurons. This modulation may operate by setting thresholds for cortical cells to the appropriate value, or by more directly influencing the cascade of processes involved in long-term potentiation [117]. There is indeed evidence that acetylcholine is necessary for cortical synaptic modifiability, as shown by studies in which depletion of acetylcholine and noradrenaline impaired cortical LTP/synaptic modifiability [118]. However, age-related damage to the basal forebrain cholinergic neurons is also likely, and with a reduction of cholinergic input, cortical neurons become much more sluggish in their responses and show much more firing rate adaptation [119, 120].The question then arises of whether the basal forebrain cholinergic neurons tonically release acetylcholine, or whether they release it particularly in response to some external influence. To examine this, recordings have been made from basal forebrain neurons, at least some of which project to the cortex [71], and some of which will have been the cholinergic neurons just described. It has been found that some of these neurons respond to visual stimuli associated with rewards, such as food [121–125], or with punishment [126]; that others respond to novel visual stimuli [127]; and that others respond to a range of visual stimuli. For example, in one set of recordings, one group of these neurons (1.5%) responded to novel visual stimuli while monkeys performed recognition or visual discrimination tasks [127]. A complementary group of neurons, located more anteriorly, responded to familiar visual stimuli in the same tasks [127, 128]. A third group of neurons (5.7%) responded to positively reinforcing visual stimuli in visual discrimination and recognition memory tasks [124, 125]. In addition, a considerable proportion of these neurons (21.8%) responded to any visual stimuli shown in the tasks, and some (13.1%) responded to the tone cue that preceded the presentation of the visual stimuli in the task, alerting the monkey to the impending visual stimuli [127]. These neurons did not respond to touch to the leg that induced arousal, so their responses did not simply reflect arousal. Neurons in this region receive inputs from the amygdala [115, 129] and orbitofrontal cortex, and it is probably via the amygdala (and orbitofrontal cortex) that the information described above reaches and activates the basal forebrain neurons. Neurons with similar response properties have been found in the amygdala, and the amygdala appears to be involved in decoding visual stimuli that are associated with reinforcers or are novel [71].

3.6.2 Acetylcholine Reduction and Impaired Synaptic Modification and Modulation

Based on this neurobiological evidence, it is therefore suggested that the normal physiological function of these basal forebrain neurons is to send a general activation signal to the cortex when certain classes of environmental stimuli occur [71]. These environmental stimuli are often the stimuli to which a behavioral response is appropriate or required, such as positively or negatively reinforcing visual stimuli or novel visual stimuli. The effect of the firing of these neurons on the cortex is excitatory and, in this way, produces activation. This cortical activation may produce arousal and may thus facilitate concentration and attention, which are both impaired in

Alzheimer's disease. The reduced arousal and concentration may contribute to the memory disorders; however, the acetylcholine released from these basal magnocellular neurons may be more directly involved in memory formation (encoding). Bear and Singer [118] showed that long-term potentiation, used as an indicator of the synaptic modification that underlies learning, requires the presence in the cortex of acetylcholine as well as noradrenaline. In a similar way, acetylcholine in the hippocampus makes it more likely that LTP will occur, probably through activation of an inositol phosphate second messenger cascade [117]. In the hippocampus and prefrontal cortex, acetylcholine may simultaneously decrease transmission in recurrent collateral excitatory connections, and this may have the beneficial effect of reducing the effects of memories already stored in the recurrent collaterals so that they do not excessively influence the neuronal firing when new memories must be stored [130]. The adaptive value of the cortical strobe provided by the basal forebrain magnocellular neurons may thus be that it facilitates memory storage, especially when significant (e.g., reinforcing) environmental stimuli are detected. This means that memory storage is likely to be conserved (new memories are less likely to be laid down) when significant environmental stimuli are not present.

It is therefore hypothesized that one way in which impaired cholinergic neuron function is likely to impair memory is by reducing the depth of the basins of attraction of hippocampal and cortical networks. Alteration of synapses that are needed for the hippocampal encoding of episodic memory and the neocortical maintenance of short-term memory is reduced. This makes both the recall of long-term episodic memories and the maintenance of short-term memory less reliable in the face of stochastic noise. This hypothesis is tested in the simulations described below by analyzing the effects on the stochastic dynamics of attractor networks by reducing NMDA receptor–activated synaptic conductances to simulate the effect of reduced synaptic connectivity.

In addition to this effect of acetylcholine on LTP, acetylcholine can act via a nicotinic receptor to enhance thalamocortical transmission [131]. At least in early cortical processing stages, this would be expected to increase cortical neuronal responses to stimuli and thereby increase attention to stimuli as well as the likelihood that the effects of the stimuli would lead to information storage. A reduction in acetylcholine in aging would thus be predicted, when acting by this mechanism, to decrease attention to and short-term memory of environmental stimuli.

In addition to these effects of acetylcholine, the neurotransmitter can also act via a nicotinic receptor to increase the firing of cortical GABA inhibitory neurons [132]. A reduction of acetylcholine in aging would thereby be expected to produce an increase in the firing of cortical excitatory neurons, and this might partially compensate for some of the other effects of reduced acetylcholine, which tend to impair the operation of short-term memory systems. This is investigated in the simulations described below and elsewhere [5].

Some of these effects of acetylcholine on the operation of cortical systems involved in attention have been investigated in a cortical model of visual processing in early cortical visual areas [133]. We investigated the effects of reductions of acetylcholine on the operation, stability, and stochasticity of cortical memory and short-term memory systems in aging in an integrate-and-fire model of these memory processes [5].

3.6.3 Acetylcholine Reduction and Spike Frequency Adaptation

Another property of cortical neurons is that they tend to adapt with repeated input [119, 120]. However, this adaptation is most marked in brain slices in which there is no acetylcholine. One effect of acetylcholine is to reduce this adaptation [134]. It appears that the afterhyperpolarization (AHP) that follows the generation of a spike in a neuron is primarily mediated by two calcium-activated potassium currents, I_{AHP} and the sI_{AHP} [135, 136], which are activated by calcium influx during action potentials. The I_{AHP} current is mediated by small conductance calcium-activated potassium (SK) channels and its time course primarily follows cytosolic calcium, rising rapidly after action potentials and decaying with a time constant of 50 to several hundred milliseconds [136]. In contrast, the kinetics of the sI_{AHP} are slower, exhibiting a distinct rising phase and decaying with a time constant of 1–2 seconds [135]. A variety of neuromodulators, including acetylcholine (ACh) (acting via muscarinic receptors), as well as noradrenaline and glutamate (acting via G-protein-coupled receptors), suppress the sI_{AHP} and thus reduce spike-frequency adaptation.

When recordings are made from single neurons operating in physiological conditions in the awake

behaving monkey, peristimulus time histograms of inferior temporal cortex neuronal responses to visual stimuli show only limited adaptation. There is typically an onset of the neuronal response at 80–100 milliseconds after the stimulus, followed within 50 milliseconds by the highest firing rate. There is afterward some reduction in the firing rate, but the firing rate is still typically more than half-maximal 500 milliseconds later [1, 137]. Thus, under normal physiological conditions, firing rate adaptation can occur but it is not large, even when cells are responding at a high rate (at, e.g., 100 spikes per second) to a visual stimulus. One of the factors that keeps the response relatively maintained may, however, be the presence of acetylcholine. Its depletion in aging and some disease states [97] could lead to less sustained neuronal responses (i.e., more adaptation), and this may contribute to the symptoms found with aging. In particular, if acetylcholine is low, the resultant reduced firing rates that may occur as a function of time would gradually, over a few hundred milliseconds, reduce the depth of the basin of attraction and thus destabilize short-term memory when noise is present, as shown in Eqn. 4. Such changes would thereby impair short-term memory and top-down attention.

The effects of this adaptation can be studied by including a time-varying intrinsic (potassium-like) conductance in the cell membrane [1, 21]. This can be done by specifying that this conductance, which if open tends to shunt the membrane and thus to prevent firing, opens by a fixed amount with the potential excursion associated with each spike, and then relaxes exponentially to its closed state. In this manner, sustained firing driven by a constant input current occurs at lower rates after the first few spikes. If the relevant parameters are set appropriately, this firing pattern is similar to the behavior observed in vitro of many pyramidal cells.

It is hypothesized that this spike frequency adaptation will reduce the depth of the basins of attraction of attractor networks involved in memory, including short-term memory, and will make the memory less reliable from trial to trial, and less robust against the effects of spiking-related and other noise. This hypothesis is tested as described below and elsewhere [5] with an implementation of the spike-frequency adaptation mechanism using Ca^{2+} activated K^{+} hyperpolarizing currents [5, 138].

3.7 Integrate-and-Fire Attractor Network Simulation Results

3.7.1 NMDA Receptor Hypofunction and Reduced Synaptic Strength

The effect of reduction in the NMDA receptor–activated channel conductances on the short-term memory performance of a simulated integrate-and-fire attractor network are shown in Figure 14.3 [5]. The network had two main populations of neurons, similar to what is shown in Figure 14.2. Population S1 was activated at time = 1–3 seconds, and then tested to see whether it reliably maintained the high firing rate in a short-term memory attractor state when the memory cue was removed at time = 3 seconds, as illustrated in Figure 14.4. This reduction simulates the effect of reduction in synaptic strength, or in the amount of glutamate released per action potential, or in the conductance of the NMDA receptor channel. It was found that a rather small reduction in synaptic strength (caused, e.g., by less efficacious LTP), or in the NMDA receptor channel conductance of 5%, causes a major reduction in the percentage of trials on which the short-term memory is maintained (Figure 14.3). The reduction also makes the spontaneous firing rate state just a little more stable. The reason that the reduction of NMDA conductance decreases the persistence of the short-term memory is that the firing rates become reduced, as illustrated in Figure 14.4, for the condition in which NMDA conductance is reduced by 5% [5]. This reduction of the firing rate decreases the depth of the basin of attraction of the short-term memory population of neurons (the "S1 pool"), and this in turn makes the short-term memory state more susceptible to the effects of the noise due to the almost Poisson firing times of the neurons, as explained elsewhere [1, 39].

The reduction in firing rate is also relevant to any effects produced in a particular neuronal population and, for example, can be reflected in hypoemotionality due to reduced firing in emotion-related states elicited by reward and nonreward in the orbitofrontal and anterior cingulate cortex [62, 71].

3.7.2 Effects of Spike Frequency Adaptation Mediated by a Reduction in Acetylcholine

Figure 14.4 also shows the effects of increasing AHP conductance (gAHP) to simulate the effects of

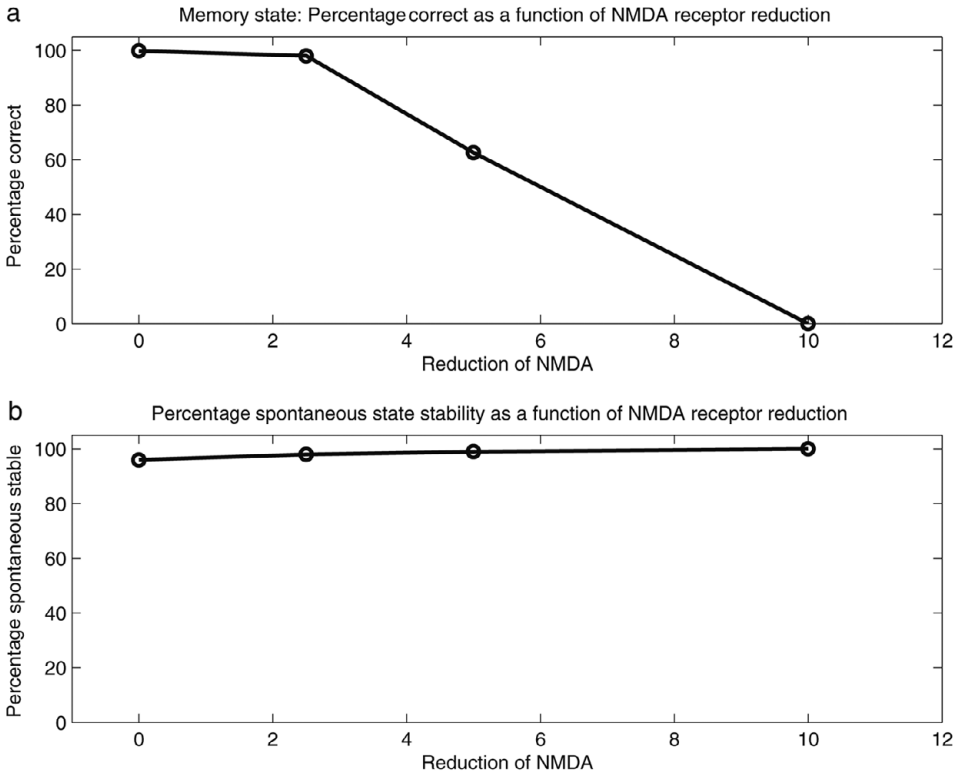

Figure 14.3 Effects of reductions of NMDA receptor conductance on short-term memory in the integrate-and-fire network. (a) The effects of different reductions of NMDA receptor conductance on the percentage of short-term memory trials that show correct short-term memory at the end of a 2-s delay period. The criterion for correct short-term memory was a firing rate in the cued pool of neurons S1 that was > 10 spikes per second higher at the end of the delay period than for the uncued pool of neurons S2. (b) The percentage of trials on which the spontaneous firing rate state was stable (with a firing rate of < 10 spikes per second) at the end of the 1-s spontaneous firing rate period (before a short-term memory cue was applied to pool S1) as a function of the reduction of NMDA receptor conductance. Each data point is based on 1,000 trials [5]. From Rolls, E.T., and G. Deco, Stochastic cortical neurodynamics underlying the memory and cognitive changes in aging. *Neurobiology of Learning and Memory*, 2015. 118: 150–161

different reductions of acetylcholine in normal aging. It is shown that when the network was in the attractor state, the firing rate was reduced. This in turn markedly reduced the persistence of short-term memory [5]. The decrease in firing rates decreases the depth of the basin of attraction and makes it more probable that the system will be knocked out of its high firing rate state by the noise related to the Poisson nature of the spike times. Superimposed on this reduction of the firing rates produced by the Ca^{2+}-mediated after-spike hyperpolarization, the gradual reduction in the firing rate, in the period of 1.0–1.5 seconds, demonstrates firing rate adaptation, which has a similar time course to that recorded in single neurons in the inferior temporal visual cortex of the awake behaving macaque [137]. Also of interest is that after the cue is removed from pool S1 at time = 3 seconds, the neurons decrease their firing rates for several hundred milliseconds, while the spike frequency adaptation recovers. During this post-cue period of reduced firing, the spike frequency adaptation mechanism makes the network especially vulnerable to being knocked out of the attractor by the spiking-dependent noise in the system.

It is thus predicted that enhancing cholinergic function is one treatment that may help to minimize the reduction in the short-term memory performance of attractor networks, involved in short-term memory and attention, that may occur in aging.

3.7.3 Reducing GABA Function When NMDA Receptor Functionality Is Reduced

The results in Figure 14.3 show that when NMDA functionality, glutamate transmission, or excitatory synaptic strength are reduced, short-term memory is impaired. This impairment appears to be related to

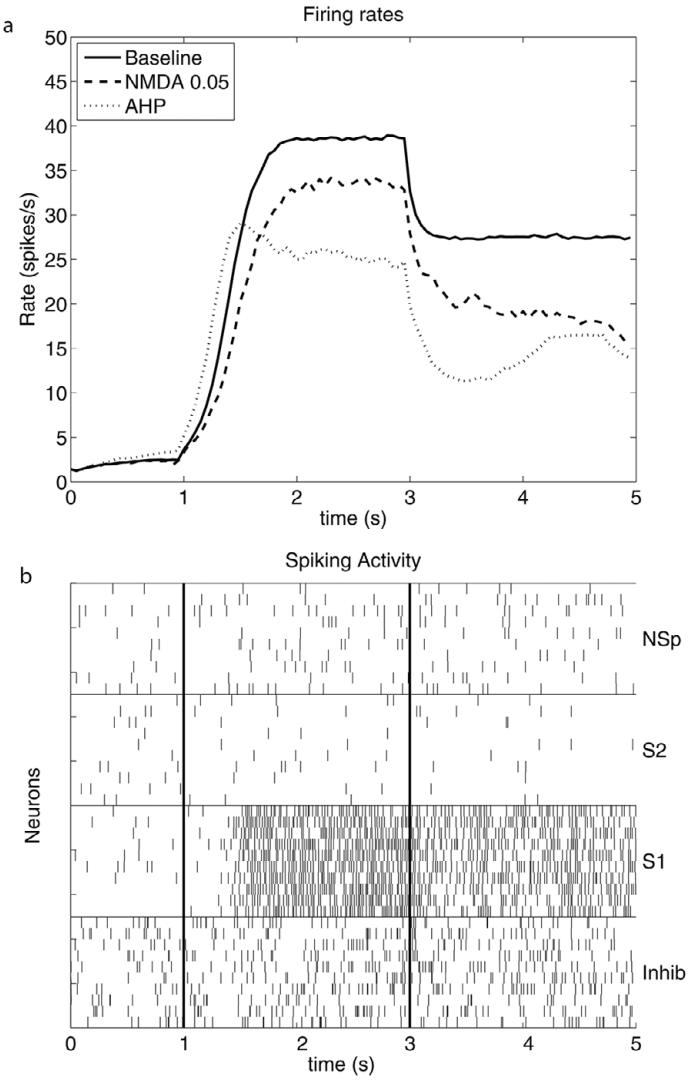

Figure 14.4 (a) Effects of reductions of NMDA receptor conductance (by 5%; NMDA 0.05) and of spike frequency adaptation (gAHP) on the firing rates of neurons in the short-term memory integrate-and-fire network. The baseline condition is with no reduction of NMDA conductances and no spike frequency adaptation. Time course: 0–1 second is spontaneous activity; 1–3 seconds is when the short-term memory cue is applied to neuron pool S1; 3–5 seconds is the period after the cue is removed and the short-term memory should be maintained by the firing rates of pool S1, which is what are shown. The firing rates are shown purely for correct trials for pool S1, that is, when the spontaneous firing state was stable and when the firing rate remained high in pool S1 (i.e., greater than 10 spikes per second more than in pool S2) until the end of the trial. The gAHP conductance was 40 nS for the AHP condition, and 0 for the other conditions. (b) Rastergrams showing the spiking activity of 10 randomly selected neurons in each pool on a typical trial for the baseline condition of no reduction in NMDA and no spike-frequency adaptation. S1, S2: the two specific pools. NSp: the nonspecific pool. Inhib: the pool of inhibitory neurons. From Rolls, E.T., and G. Deco, Stochastic cortical neurodynamics underlying the memory and cognitive changes in aging. *Neurobiology of Learning and Memory*, 2015. 118: 150–161

the fact that the reduced firing rates and depths of the basins of attraction result in failure to maintain the firing of the cued attractor. Thus, the memory, and any attentional effect maintained by it, is frequently lost. Would a reduction of inhibitory transmission mediated by GABA reduction alleviate this problem, by allowing the firing rates to remain high in a cued attractor after the cue is removed? It was shown that a reduction by 10% in the GABA synaptic conductance can at least partially help the memory to be maintained [5]. However, the effects of the reduction of GABA to help maintain a cued high firing rate attractor short-term memory state comes at a cost. It was found that the reduced inhibition produced by a 10% reduction in GABA causes the spontaneous firing rate state (i.e., before the recall cue is applied) to frequently become unstable. The instability was evident in that, even when no recall cue was applied, the network would sometimes jump from the spontaneous firing rate state to a high firing rate state, provoked by the spiking-related noise in the system. Thus, simply reducing the inhibition in the system to compensate for the decreased excitatory synaptic transmission in aging may not be a useful approach to treatment. This is because of the risk that the spontaneous firing rate state, when no stimuli are applied, will become unstable, such that the network jumps into a state of high firing. This reduced inhibition could increase the risk of disorders such as hallucinations or epilepsy.

3.8 Implications

The reduced depth in the basins of attraction that the different neurobiological mechanisms produce in relation to normal aging could have a number of effects that are relevant to the cognitive changes in aging:

First, the stability of short-term memory networks would be impaired, and it might be difficult to hold items in short-term memory for a long period, as the noise might more easily push the network out of its shallow attractor.

Second, top-down attention would be impaired, in two ways. First, the short-term memory network holding the object of attention in mind would be less stable, so that the source of the top-down bias for the biased competition in other cortical areas might disappear. Second, even when the short-term memory for attention is still in its persistent attractor state, it would be less effective as a source of the top-down bias because the firing rates would be lower, as shown in Figure 14.4.

Third, the recall of information from episodic memory systems, such as object-place memory [1], would be impaired. This would arise because the positive feedback from the recurrent collateral synapses that helps the system to fall into a basin of attraction, representing in this case the recalled memory, would be less effective. The network would be more noisy overall, and in particular, the attractor state would not be maintained for the several seconds necessary for the recalled memory to be used.

Fourth, any reduction of the firing rate of the pyramidal cells caused by NMDA receptor hypofunction would itself be likely to impair new learning involving LTP.

In addition, if the NMDA receptor hypofunction were expressed not only in the prefrontal cortex, where it would affect short-term memory, and in the temporal lobes, where it would affect episodic memory [1], but also in the orbitofrontal cortex, then we would predict some reduction in emotion and motivation with aging, as these functions rely on the orbitofrontal cortex [63, 71], where there would be a reduction in firing rate due to the NMDA receptor hypofunction.

Although a decrease of GABA efficacy may help to maintain a network in an attractor state when NMDA receptor–mediated effects are reduced, this comes at the cost of reducing the stability of the spontaneous firing state when no cues are applied [5]. The effect of instability in the spontaneous firing rate state when no stimuli are applied is that the network enters one of its high firing rate attractor states even without any external input. This would increase the risk, for example, of hallucinations or epilepsy. Thus, reducing inhibition is likely to be an unsafe way, in terms of stochastic neurodynamics, to treat the short-term memory and attentional problems in aging. Instead, a better approach would be to use treatments that would increase the excitatory glutamatergic transmission in cortical networks. This might (after careful and full testing) involve effects such as that of glycine in upwardly modulating the NMDA receptor [139]; agents such as AMPAkines that increase transmission through effects on the AMPA glutamatergic receptors [139]; agents that mimic dopaminergic or cholinergic effects; or other types of stimulants, including perhaps caffeine. Indeed, one of the advantages of the stochastic neurodynamics approach is that it allows combinations of such approaches to be tested, allowing exploration of approaches where any one agent is in low concentration to minimize any side effects. Part of the interest of this stochastic dynamics approach to aging is that it provides a way to test treatments and combinations of pharmacological treatments that may together help to minimize the cognitive symptoms and signs of aging. The approach facilitates the investigation of drug combinations that may together be effective in doses lower than when only one drug is given. Further, this approach may lead to predictions for effective treatments that need not necessarily restore the particular change in the brain that caused the symptoms, but may engage alternative routes to restore the stability of the dynamics. For example, nicotine (self-administered by gum or patch) might increase the firing rates of neurons in some of the relevant brain systems, and this might ameliorate some of the symptoms. Consistent with this proposal, nicotinic stimulation may improve cognition and neural functioning and may also elevate mood in depression [140, 141], both of which are predicted from the effects described here of acetylcholine on the stability of memory networks in the prefrontal cortex and hippocampus, as well as on the firing rates of neurons in areas such as the orbitofrontal and anterior cingulate cortex involved in emotion and mood.

In the context of normal aging, if the depth of the basins of attraction is impaired by one of more of the

mechanisms described above, then this might have an effect on decision-making systems of the type illustrated in Figure 14.2. In these circumstances, decisions might become noisier, that is, less closely related to the decision variables; slower; and they might not be maintained well in the short term. Planning related to the decision would not necessarily be maintained as persistently as with unreduced depths of the basins of attraction. This is an idea that arises from considering this type of decision-making system, and it would be of interest to explore this proposal further.

Finally, although the research described here has focused on attentional and short-term memory changes in normal aging, the results are also relevant to the preclinical changes in Alzheimer's disease, in which synaptic transmission and plasticity in NMDA receptors may be reduced because of effects related to soluble Aβ oligomers [142].

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