Stochastic cortical neurodynamics underlying the memory and cognitive changes in aging

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Abstract

The relatively random spiking times of individual neurons provide a source of noise in the brain. We show how this noise interacting with altered depth in the basins of attraction of networks involved in short-term memory, attention, and episodic memory provide an approach to understanding some of the cognitive changes in normal aging. The effects of the neurobiological changes in aging that are considered include reduced synaptic modification and maintenance during learning produced in part through reduced acetylcholine in normal aging, reduced dopamine which reduces NMDA-receptor mediated effects, reduced noradrenaline which increases cAMP and thus shunts excitatory synaptic inputs, and the effects of a reduction in acetylcholine in increasing spike frequency adaptation. Using integrate-and-fire simulations of an attractor network implementing memory recall and short-term memory, it is shown that all these changes associated with aging reduce the firing rates of the excitatory neurons, which in turn reduce the depth of the basins of attraction, resulting in a much decreased probability in maintaining in short-term memory what has been recalled from the attractor network. This stochastic dynamics approach opens up new ways to understand and potentially treat the effects of normal aging on memory and cognitive functions.

Key words: aging; cortical attractor networks; memory; acetylcholine; NMDA receptors
1 Introduction: stochastic noise, attractor dynamics, and aging

Cognitive symptoms such as poor short-term memory and attention could arise due to reduced depth in the basins of attraction of prefrontal cortical networks, and the effects of noise (Loh, Rolls and Deco 2007a, Loh, Rolls and Deco 2007b, Rolls, Loh and Deco 2008a, Rolls and Deco 2010, Rolls and Deco 2011). 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. Given that top-down attention requires a short-term memory to hold the object of attention in mind, and that this is the source of the top-down attentional bias that influences competition in other networks that are receiving incoming signals, then disruption of short-term memory is also predicted to impair the stability of attention, and many cognitive and executive functions that depend on the stability of short-term memory. These ideas are elaborated elsewhere (Loh et al. 2007a, Loh et al. 2007b, Rolls et al. 2008a, Rolls 2008a, Rolls and Deco 2010, Rolls and Deco 2011, Rolls 2014a), where the reduced depth of the basins of attraction in schizophrenia is related to down-regulation of NMDA receptors, or to factors that influence NMDA receptor generated ion channel currents such as dopamine D1 receptors.

In this paper we consider the hypothesis that the impairments in short-term memory and attention that are common in normal aging occur because the stochasticity of the dynamics is increased because of a reduced depth in the basins of attraction of cortical attractor networks involved in short-term memory and attention. Reduced short-term memory and less good attention are common in aging, as are impairments in episodic memory (Grady 2008). Short-term memory and attention are related to the operation of the dorsolateral prefrontal cortex (Goldman-Rakic 1996, Fuster 2008, Miller and Cohen 2001, Miller 2013, Arnsten 2013) using attractor networks which also provide the source of the top-down attentional bias (Rolls and Deco 2002, Deco and Rolls 2003, Deco and Rolls 2005a, Rolls 2008a, Grabenhorst and Rolls 2010, Ge, Feng, Grabenhorst and Rolls 2012, Luo, Ge, Grabenhorst, Feng and Rolls 2013). Episodic memory utilizes attractor networks in the hippocampus (Rolls 2008a, Rolls 2010, Rolls 2013b, Rolls 2013a, Rolls 2014b). 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 evidence on the neurobiology of normal aging (Samson and Barnes 2013, Schliebs and Arendt 2011), an aim of the present approach is to provide a mechanistic, computational neuroscience, stochastic neurodynamics framework (Rolls 2008a, Rolls and Deco 2010) for analysis of how the operation of cortical memory circuits involved in short-term memory, attention, and episodic memory, are altered by these changes. This in turn has implications for how to ameliorate the changes in the operation of cortical networks during normal aging.
2 Neurodynamical hypotheses based on the neurobiology of aging

2.1 NMDA receptor hypofunction

One change in aging is that NMDA receptor functionality tends to decrease in aging (Kelly, Nadon, Morrison, Thibault, Barnes and Blalock 2006). This would act, as investigated elsewhere (Loh et al. 2007a, Rolls et al. 2008a), to reduce the depth of the basins of attraction, both by reducing the firing rate of the neurons in the active attractor, and effectively by decreasing the strength of the potentiated synaptic connections that support each attractor as the currents passing through these potentiated synapses would decrease.

The reduced depth of the basins of attraction can be understood in more detail in the following way (see also Rolls and Deco (2010)). Hopfield (1982) showed that the recall state in an attractor network can be thought of as the local minimum in an energy landscape, where the energy would be defined as

\[ E = -\frac{1}{2} \sum_{i,j} w_{ij} (y_i - < y >)(y_j - < y >) \] (1)

where \( y_i \) and \( y_j \) are the firing rates of the \( i \)'th and \( j \)'th neurons in the network, which are connected by synaptic weight \( w_{ij} \), and \( < y > \) is the mean firing rate of the neurons. In general neuronal systems do not admit an energy function. Nevertheless, we can assume an effective energy function: in fact, the flow diagram shown by Loh, Rolls and Deco (2007a) resulting from the mean-field reduction associated with the spiking network analyzed, can be viewed as an indirect description of an underlying effective energy function. From this equation, it follows that the depth of a basin of attraction is deeper if the firing rates are higher and if the synaptic strengths that couple the neurons that are part of the same attractor are strong. (The negative sign results in a low energy, and thus a stable state, if the firing rates of the neurons in the same attractor and their synaptic coupling weights are high.) If we reduce the NMDA receptor activated channel conductances, then the depth of the basins of attraction will be reduced both because the firing rates are reduced by reducing excitatory inputs to the neurons, and because the synaptic coupling weights are effectively reduced because the synapses can pass only reduced currents.

We therefore hypothesize that in normal aging, short-term memory and attention will be impaired because the basins of attraction of the prefrontal cortex attractor networks mediating these functions (Goldman-Rakic 1996, Wang, Yang, Wang, Gamo, Jin, Mazer, Morrison, Wang and Arnsten 2013, Arnsten and Jin 2014) will have a reduced depth, will therefore be less stable, and this will result in an increased proportion of trials on which the short-term memory will not be maintained. Similarly, we hypothesize that in aging, episodic memory will be impaired because the basins of attraction of the hippocampal attractor networks mediating these functions (Rolls 2010, Rolls 2013b, Rolls 2013a) will have a reduced depth, will therefore be less stable, and this will result in an increased proportion of trials on which the episodic memory will not be correctly recalled and maintained active for a short period while they are used. These neurodynamical hypotheses are tested in the Results section.
2.2 Dopamine

D1 receptor blockade in the prefrontal cortex can impair short-term memory (Sawaguchi and Goldman-Rakic 1991, Sawaguchi and Goldman-Rakic 1994, Goldman-Rakic 1999, Castner, Williams and Goldman-Rakic 2000). Part of the reason for this may be that D1 receptor blockade can decrease NMDA receptor activated ion channel conductances, among other effects (Seamans and Yang 2004, Durstewitz, Kelc and Gunturkun 1999, Durstewitz, Seamans and Sejnowski 2000, Brunel and Wang 2001, Durstewitz and Seamans 2002). 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 (Loh, Rolls and Deco 2007a, Loh, Rolls and Deco 2007b, Rolls, Loh, Deco and Winterer 2008b). 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 equation 1). The reduced depth of the basins of attraction can be thought of as decreasing the signal-to-noise ratio (Loh, Rolls and Deco 2007b, Rolls, Loh, Deco and Winterer 2008b). Given that dopaminergic function in the prefrontal cortex may decline with aging (Sikström 2007), and in conditions in which there are cognitive impairments such as Parkinson’s disease, the decrease in dopamine could contribute to the reduced short-term memory and attention in aging.

In attention deficit hyperactivity disorder (ADHD), in which there are attentional deficits including too much distractibility, catecholamine function more generally (dopamine and noradrenaline (i.e. norepinephrine)) may be reduced (Arnsten and Li 2005), and these reductions could produce less stability of short-term memory and thereby attentional states by reducing the depth of the basins of attraction.

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 (Diamond 1996). These effects may also be related to an effect of dopamine acting for example via NMDA receptors to increase neuronal firing rates and thus the stability of short-term memory attractor networks.

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 is tested in the Results section.

Investigations in macaques that are not old emphasize that providing extra D1 receptor stimulation beyond that naturally present by iontophoresing D1R agonist onto a prefrontal cortex neuron can produce suppression of neuronal firing (Vijayraghavan, Wang, Birnbaum, Williams and Arnsten 2007), consistent with the evidence that D1R stimulation has an inverted U dose-response effect, with high doses producing suppression (Seamans and Yang 2004). This may contribute to a process by which stress that elevates dopamine levels (Rolls 2014a) can impair memory functions. By reducing the firing rate of the neuron, the D1R agonist (acting to increase the cAMP signalling described in the next section) can at moderate doses increase the ratio of the neuronal response to the preferred stimulus relative to the response to the non-preferred stimulus (Vijayraghavan et al. 2007). At high doses, all the firing is greatly reduced, and finally the ratio decreases. Indeed, a similar effect has been described in the striatum, where iontophoresis of dopamine reduced neuronal firing rates, so that the response of the neuron expressed as a ratio relative to the spontaneous firing rate can actually increase at moderate doses (Rolls, Thorpe, Boytim, Szabo and Perrett 1984).
2.3 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 cAMP (Wang, Ramos, Paspalas, Shu, Simen, Duque, Vijayaraghavan, Brennan, Dudley, Nou, Mazer, McCormick and Arnsten 2007). cAMP closes Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels. The HCN channels on the distal dendrites allow $K^+$ (and $Na^+$) to pass through generating an $h$ current ($I_h$) that shunts the effects of synaptic inputs (He, Chen, Li and Hu 2014), including inputs from the recurrent collateral connections. Thus the 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 came from iontophoresis of agents that influence these cAMP-activated HCN channels onto single neurons in the macaque dorsolateral prefrontal cortex (Wang et al. 2007).

Noradrenaline reaches the cortex from the locus coeruleus, and a reduction in noradrenaline in aging and mild cognitive impairment (Grudzien, Shaw, Weintraub, Bigio, Mash and Mesulam 2007), together with a loss of alpha2A adrenoceptors in the aged prefrontal cortex (Moore, Schettler, Killiany, Herndon, Luebke, Moss and Rosene 2005), and decreased excitation of noradrenergic neurons (Downs, Dunn, Borok, Shanabrough, Horvath, Kohama and Urbanski 2007), would thus tend to impair short-term memory. The effect is modelled in the simulations described below by decreasing the synaptic input associated with the recurrent collaterals by reducing the NMDA synaptic conductance in the recurrent collaterals (see Section 4.1). 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 thus predicts the changes in the firing rates that were found experimentally (Wang et al. 2007).

Although this may or may not be due only to changes in the noradrenergic system in aging, the loss of persistent firing is related to increased cAMP-K+ channel signaling (Wang, Gamo, Yang, Jin, Wang, Laubach, Mazer, Lee and Arnsten 2011), arising from a loss of PDE4A (Carlyle, Nairn, Wang, Yang, Jin, Simen, Ramos, Bordner, Craft, Davies, Pletikos, Sestan, Arnsten and Paspalas 2014). The loss of PDE4A leads to hyperphosphorylation of tau and vulnerability to degeneration, an effect that is most relevant to Alzheimer’s Disease.

2.4 Impaired synaptic modification

Another factor that may contribute to the memory and cognitive changes in 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 (Barnes 2003, Burke and Barnes 2006, Kelly et al. 2006, Samson and Barnes 2013). This would tend to make the synaptic strengths that would support an attractor weaker, and weaken further over the course of time, and thus directly reduce 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 (Rolls 2008a, Rolls 2008b, Dere, Easton, Nadel and Huston 2008, Rolls 2010). The reduction of synaptic strength over time could also affect short-term memory, which requires that the synapses that support a short-term memory attractor be modified in the first place using LTP, before the attractor is used (Kesner and Rolls 2001).
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 potentiator agents have been explored in rodent models and have entered clinical trials (Lynch and Gall 2006, O’Neill and Dix 2007). 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 (Thibault, Porter, Chen, Blalock, Kaminker, Clodfelter, Brewer and Landfield 1998, Kelly et al. 2006). In particular, an increase in Ca$_{2+}$ conductance can occur in aged neurons, and 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 (Burke and Barnes 2006).

The neurodynamical hypothesis that in aging impaired synaptic modification during learning and/or poorer maintenance of synaptic modification after learning could impair episodic memory, and short-term memory and related attentional and executive functions, is tested in the Results section, by analysing the effects on the stochastic dynamics of attractor networks of reducing NMDA receptor activated synaptic conductances, to simulate the effect of less strong synapses.

Reduced synaptic modifiability and the effects of synaptic modification might or might not be reflected in the expression of NMDA and AMPA receptors during aging, and we do not explicitly hypothesize that there is a change, nor was it an aim to investigate it here. However, we do note that in aged compared to young macaques it has been reported that there is a reduction in the proportions of neurons in areas such as the parietal, prefrontal, and temporal cortex with immunohistochemically measurable expression of NMDAR1 receptors (by 30.6%) and of AMPA (GluR2) receptors (by 29.2%) (Hof, Duan, Page, Einstein, Wicinski, He, Erwin and Morrison 2002). We simply note here that if those changes did reflect synaptic strengths, that hypothesis is tested by the effects of the reductions of NMDA receptor conductances described in Section 4.1, which reduced the stability of the short-term memory in the delay period.

2.5 Cholinergic function

2.5.1 Acetylcholine in the cortex and aging

Another change in 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 (Mesulam 1990). 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 as well as levels of acetylcholine, suggested an association of cholinergic hypofunction with cognitive deficits, which led to the formulation of the cholinergic hypothesis of memory dysfunction in senescence and in Alzheimer’s disease (Bartus 2000, Schliebs and Arendt 2006). In this section we 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 in cognitive functions that depend on short-term memory such as attention. For top-down attention, the subject of attention must be

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 (Mesulam 1990). These cells, many but not all of which are cholinergic (Baxter and Bucci 2013), project directly to the cerebral cortex (Divac 1975, Kievit and Kuypers 1975, Mesulam 1990). These cells provide the major cholinergic input to the cerebral cortex, in that if they are lesioned the cortex is depleted of acetylcholine (Mesulam 1990). Loss of these cells does occur in Alzheimer’s disease, and there is consequently a reduction in cortical acetylcholine in this disease (Mesulam 1990, Schliebs and Arendt 2006). This loss of cortical acetylcholine may contribute to the memory loss in Alzheimer’s disease, although it may not be the primary factor in the aetiology.

It has been shown that damage to the basal forebrain cholinergic neurons can impair attention and short-term memory. Impairments on a simple test of recognition memory, delayed non-match-to-sample, were produced by neurotoxic lesions of this region in monkeys (Aigner, Mitchell, Aggleton, DeLong, Struble, Price, Wenk, Pettigrew and Mishkin 1991). Similar lesions in rats impaired performance on memory tasks, perhaps because of failure to attend properly (Muir, Everitt and Robbins 1994). Damage to the cholinergic neurons in this region in monkeys with a selective immunotoxin has also been shown to impair processes that require the maintenance of a short-term memory such as attention (Baxter and Bucci 2013).

There are quite limited numbers of these basal forebrain neurons (in the order of thousands). Given that there are relatively few of these neurons, it is not likely that they carry the information to be stored in cortical memory circuits, for 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 on to each neuron in a pattern associator, see e.g. Rolls (2008a)). With these few neurons distributed throughout the cerebral cortex, the memory capacity of the whole system would be impractically small. This argument alone indicates that they are unlikely to carry the information to be stored in cortical memory systems. Instead, they could modulate storage in the cortex of information derived from what provides the numerically major 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 (Rolls 2008a, Hasselmo and Sarter 2011). 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 (Bear and Singer 1986). However, non-specific effects of damage to the basal forebrain cholinergic neurons are also likely, with cortical neurons becoming much more sluggish in their responses, and showing much more firing rate adaptation, in the absence of cholinergic inputs (Fuhrmann, Markram and Tsodyks 2002, Abbott, Varela, Sen and Nelson 1997) (see below).

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 (see Rolls (2005)), 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 (Rolls 1990, Rolls 1993, Rolls, Burton and Mora 1976, Burton, Rolls and Mora 1976, Mora, Rolls and Burton 1976, Wilson and Rolls 1990b, Wilson and Rolls 1990a), or with punishment (Rolls, Sanghera and Roper-
Hall 1979), that others respond to novel visual stimuli (Wilson and Rolls 1990c), 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 (Wilson and Rolls 1990c). A complementary group of neurons more anteriorly responded to familiar visual stimuli in the same tasks (Rolls, Perrett, Caan and Wilson 1982, Wilson and Rolls 1990c). A third group of neurons (5.7%) responded to positively reinforcing visual stimuli in visual discrimination and in recognition memory tasks (Wilson and Rolls 1990b, Wilson and Rolls 1990a). 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, and was provided to enable the monkey to alert to the visual stimuli (Wilson and Rolls 1990c). These neurons did not respond to touch to the leg which induced arousal, so their responses did not simply reflect arousal. Neurons in this region receive inputs from the amygdala (see Mesulam (1990); Amaral, Price, Pitkanen and Carmichael (1992); Rusinghen, Amaral and Price (1985)) and orbitofrontal cortex, and it is probably via the amygdala (and orbitofrontal cortex) that the information described here reaches the basal forebrain neurons, for 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 (Rolls 1990, Rolls 1992, Rolls 2000, Wilson and Rolls 1993, Wilson and Rolls 2005, Rolls 2005, Rolls 2008a, Rolls 2014a).

2.5.2 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. These stimuli are often stimuli to which behavioural activation 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 behavioural arousal, and may thus facilitate concentration and attention, which are both impaired in Alzheimer’s disease. The reduced arousal and concentration may themselves contribute to the memory disorders. But the acetylcholine released from these basal magnocellular neurons may in addition be more directly necessary for memory formation, for Bear and Singer (1986) showed that long-term potentiation, used as an indicator of the synaptic modification which 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 (Markram and Segal 1990, Markram and Segal 1992, Seigel and Auerbach 1996, Hasselmo and Bower 1993, Hasselmo, Schnell and Barkai 1995, Giocomo and Hasselmo 2007, Hasselmo and Sarter 2011). 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 influence too much the neuronal firing when new memories must be stored (Giocomo and Hasselmo 2007, Rolls 2013a).

The adaptive value of the cortical strobe provided by the basal 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 cortical (including hippocampal) networks, in that these networks have less strong modification during learning of the synapses that are needed for episodic memory in the hippocampus and for short-term memory in the neocortex, thus making the recall of long-term episodic memories less reliable in the face of stochastic noise, and the maintenance of short-term memory less reliable in the face of stochastic noise. This hypothesis is tested in the Results section, by analysing the effects on the stochastic dynamics of attractor networks by reducing NMDA receptor activated synaptic conductances, to simulate the effect of less strong synapses.

In addition to this effect of acetylcholine on LTP, acetylcholine can act via a nicotinic receptor to enhance thalamo-cortical transmission (Gil, Connors and Amitai 1997). At least in early cortical processing stages, this would be expected to increase cortical neuronal responses to stimuli, and thereby increase attention to stimuli, and the likelihood that the effects of the stimuli would activate and be stored in memory systems. 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, it can also act via a nicotinic receptor to increase the firing of cortical GABA inhibitory neurons (Disney, Domakonda and Aoki 2006). A reduction of acetylcholine in aging would 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 memory including short-term memory systems. This is investigated in Section 4.3.

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 (Deco and Thiele 2011). Here we investigate in particular and in contrast the effects of reductions of acetylcholine on the operation and especially on the stability and stochasticity of cortical memory and short-term memory systems in aging in an integrate-and-fire model of these memory processes.

2.5.3 Acetylcholine reduction and spike frequency adaptation

Another property of cortical neurons is that they tend to adapt with repeated input (Abbott et al. 1997, Fuhrmann et al. 2002). However, this adaptation is most marked in slices, in which there is no acetylcholine. One effect of acetylcholine is to reduce this adaptation (Power and Sah 2008). The mechanism is understood as follows. The afterpolarization (AHP) that follows the generation of a spike in a neuron is primarily mediated by two calcium-activated potassium currents, $I_{AHP}$ and the $sI_{AHP}$ (Sah and Faber 2002), 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 (Sah and Faber 2002). In contrast, the kinetics of the $sI_{AHP}$ are slower, exhibiting a distinct rising phase and decaying with a time constant of 1–2 s (Sah 1996). A variety of neuromodulators, including acetylcholine (ACh) acting via a muscarinic receptor, noradrenaline, and glutamate acting via G-protein-coupled receptors, suppress the $sI_{AHP}$ and
thus reduce spike-frequency adaptation (Nicoll 1988).

When recordings are made from single neurons operating in physiological conditions in the awake behaving monkey, peristimulus time histograms of inferior temporal cortex neurons to visual stimuli show only limited adaptation. There is typically an onset of the neuronal response at 80–100 ms after the stimulus, followed within 50 ms by the highest firing rate. There is after that some reduction in the firing rate, but the firing rate is still typically more than half-maximal 500 ms later (see example in Tovee, Rolls, Treves and Bellis (1993)). Thus under normal physiological conditions, firing rate adaptation can occur, but does not involve a major adaptation, even when cells are responding fast (at e.g. 100 spikes/s) 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 (Schliebs and Arendt 2006) could lead to less sustained neuronal responses (i.e. more adaptation), and this may contribute to the symptoms found. In particular, the reduced firing rate that may occur as a function of time if acetylcholine is low 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, by reducing the firing rate component shown in equation 1. Such changes would thereby impair short-term memory, and thus also top-down attention.

The effects of this adaptation can be studied by including a time-varying intrinsic (potassium-like) conductance in the cell membrane (Brown, Gähwiler, Griffith and Halliwell 1990, Treves 1993, Rolls 2008a). 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, in a way similar, if the relevant parameters are set appropriately, to the behaviour observed in vitro of many pyramidal cells (for example, Lanthorn, Storm and Andersen (1984), Mason and Larkman (1990)).

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 therefore less reliable from trial to trial, and less robust against the effects of spiking-related and other noise. This hypothesis is tested in the Results section, with an implementation of the spike-frequency adaptation mechanism using Ca$^{2+}$-activated K$^+$ hyper-polarizing currents (Liu and Wang 2001, Deco and Rolls 2005b, Deco and Rolls 2005c) that is described in the Methods and Supplementary Material.

3 Methods

3.1 Attractor Framework

Our aim is to investigate stability and distractibility in a biophysically realistic attractor framework, so that the properties of receptors, synaptic currents and the statistical effects related to the probabilistic spiking of the neurons can be part of the model. We use a minimal architecture, a single attractor or autoassociation network (Hopfield 1982, Amit 1989, Hertz, Krogh and Palmer 1991, Rolls and Treves 1998, Rolls and Deco 2002, Rolls 2008a). We chose a recurrent (attractor) integrate-and-fire network model which includes synaptic channels for AMPA, NMDA and GABA$_A$ receptors (Brunel and Wang 2001).

Both excitatory and inhibitory neurons are represented by a leaky integrate-and-fire model (Tuckwell 1988). The basic state variable of a single model neuron is the membrane potential.
It decays in time when the neurons receive no synaptic input down to a resting potential. When synaptic input causes the membrane potential to reach a threshold, a spike is emitted and the neuron is set to the reset potential at which it is kept for the refractory period. The emitted action potential is propagated to the other neurons in the network. The excitatory neurons transmit their action potentials via the glutamatergic receptors AMPA and NMDA which are both modeled by their effect in producing exponentially decaying currents in the postsynaptic neuron. The rise time of the AMPA current is neglected, because it is typically very short. The NMDA channel is modeled with an alpha function including both a rise and a decay term. In addition, the synaptic function of the NMDA current includes a voltage dependence controlled by the extracellular magnesium concentration (Jahr and Stevens 1990). The inhibitory postsynaptic potential is mediated by a GABA_A receptor model and is described by a decay term.

The single attractor network contains 800 excitatory and 200 inhibitory neurons, which is consistent with the observed proportions of pyramidal cells and interneurons in the cerebral cortex (Abeles 1991, Braitenberg and Schütz 1991). The connection strengths are adjusted using mean-field analysis (Brunel and Wang 2001, Rolls and Deco 2010), so that the excitatory and inhibitory neurons exhibit a spontaneous activity of 3 Hz and 9 Hz, respectively (Wilson, O’Scalaidhe and Goldman-Rakic 1994, Koch and Fuster 1989). The recurrent excitation mediated by the AMPA and NMDA receptors is dominated by the NMDA current to avoid instabilities during the delay periods (Wang 2002).

Our cortical network model features a minimal architecture to investigate stability of recalled memories in a short-term memory period, and consists of two selective pools S1 and S2 (Fig. 1). We use just two selective pools to eliminate possible disturbing factors. The non-selective pool NS models the spiking of cortical neurons and serves to generate an approximately Poisson spiking dynamics in the model (Brunel and Wang 2001), which is what is observed in the cortex. The inhibitory pool IH contains the 200 inhibitory neurons. The connection weights between the neurons within each selective pool or population are called the intra-pool connection strengths \( w_+ \). The increased strength of the intra-pool connections is counterbalanced by the other excitatory connections \( (w_-) \) to keep the average input constant.

The network receives Poisson input spikes via AMPA receptors which are envisioned to originate from 800 external neurons at an average spontaneous firing rate of 3 Hz from each external neuron, consistent with the spontaneous activity observed in the cerebral cortex (Wilson et al. 1994, Rolls and Treves 1998, Rolls 2008a). A detailed mathematical description is provided in the Supplementary Material.

3.2 Spike frequency adaptation mechanism

A specific implementation of the spike-frequency adaptation mechanism using \( \text{Ca}^{2+} \)-activated K\(^+\) hyper-polarizing currents (Liu and Wang 2001) was implemented, and is described in the Supplementary Material. Its parameters were chosen to produce spike frequency adaptation similar in timecourse to that found in the inferior temporal visual cortex of the behaving macaque (Tovee et al. 1993). In particular, \( [\text{Ca}^{2+}] \) is initially set to be 0 \( \mu \text{M} \), \( \tau_{\text{Ca}} = 300 \text{ ms} \), \( \alpha = 0.002 \), \( V_K = -80 \text{ mV} \) and \( g_{\text{AHP}}=0\text{--}40 \text{ nS} \). \( g_{\text{AHP}} = 0 \text{ nS} \) simulates the effect of high levels of acetylcholine producing alertness and attention, and \( g_{\text{AHP}} = 40 \text{ nS} \) simulates the effect of low levels of acetylcholine in normal aging that produces spike frequency adaptation.
3.3 Analysis

The correct retrieval of a memory from the network, and its maintenance in short-term memory for subsequent use, was investigated in integrate-and-fire simulations with the following protocol for each trial, which is illustrated in Fig. 2.

A spontaneous firing rate period was from 0–1 s with no memory cue applied. The input firing rate was a Poisson spike train at 3.0 spikes/s to each of the 800 synapses on every neuron in the simulation. Stability of the memory system against the statistical fluctuations caused by the Poisson inputs to the neurons and the spiking in the network was measured by the criterion that the mean firing rate should be less than 5 spikes/s in both pools S1 and S2 for the last 0.5 s of the spontaneous period. (The mean spontaneous rate had been set to be 3 spikes/s for an infinite size system with no statistical fluctuations using a mean-field analysis (Brunel and Wang 2001, Rolls and Deco 2010)). The baseline example trial shown in Fig. 2 (top) shows correct stability, and the trial in Fig. 2 (bottom) shows an example of a trial in which the spontaneous state was not stable, and a high firing rate state for pool S1 was reached before the memory retrieval cues were applied at time = 1 s.

The memory cue was applied for the period 1–3 s by increasing the mean input to each of the 800 synapses on every neuron in pool S1 to 3.06 spikes/s. The baseline example trial shown in Fig. 2 (top) shows that during the period 1-3 s the application of this memory cue resulted in a high firing rate state (of approximately 40 spikes/s) for the neurons in pool S1. (The mean rate across 1000 correct trials is shown in Fig. 4.) This is an attractor state, for the high firing rate is not achieved immediately that the memory retrieval cue is applied, but only after a time of typically 100–200 ms, as illustrated in Figs. 2 and 4. Sometimes, due to instability in the spontaneous period or due to incorrect retrieval in the cue period the wrong population of neurons, pool S2, fired at a high rate, and this was counted as a memory failure trial.

For the period 3–5 s the memory retrieval cue was no longer present (i.e. the input firing rate to every synapse on every neuron in pool S1 reverted to 3.0 spikes/s), and the maintenance of a correct retrieved memory was measured as reflected in a continuing high firing rate attractor state of the cued neuronal pool, S1. The firing rates on a single trial for the 80 neurons in pool S1 are shown for a correct trial showing baseline performance in Fig. 2 (top) and across 1000 trials in Fig. 4 (Baseline). Middle. A trial on which the short-term memory failed after the cue was removed, and the firing rate fell back to the spontaneous firing rate, is illustrated in Fig. 2 (middle). The criterion for failure of the memory to be correctly retrieved and maintained was a mean rate for pool S1 that was not 10 or more spikes/s higher than for pool S2 in the period 4–5 s.

Before the integrate-and-fire simulations were performed, mean-field analyses were performed to establish the key parameters of the system that would result in correct attractor stable states for the spontaneous firing rate period (low firing), and for the memory maintenance period (time=3–5 s in these simulations, when firing should be at a high rate). These mean field analyses resulted in the key parameters being chosen to be the following: $w_+ = 2.1$. (This is the strength of the recurrent synapses between the excitatory neurons within each of the 2 specific excitatory pools, namely S1 and S2, as illustrated in Fig. 1. This in turn led to the value for $w_-$ (the excitatory connection strengths to excitatory neurons in other pools) of 0.878, as described in the Supplementary Material.) All other synaptic connection strengths were set to 1.0, as shown in Fig. 1. The mean-field analysis also led to the choice of the mean Poisson input to each synapse in the network being 3.0 spikes/s when a specific
pool was not being cued with a memory retrieval cue.

This protocol enabled measurement of how the system performed in the baseline condition, but also in particular how the system operated when the effects of neuronal parameters affected by aging on the memory performance were being investigated. The first type of change made was to reduce parametrically the conductance of the NMDA receptors in the system. This not only tests the effect of reducing the NMDA conductances, one of the changes associated with aging (Section 2.1), but also the strengths of the excitatory connections between neurons, which may become weaker due for example to reduction in the magnitude and maintenance of LTP in aging (Section 2.4). Altering this parameter also tests the hypothesis about the effects of reduction of dopaminergic function mediated through D1 receptors in aging, for this reduces NMDA receptor conductances, as described in Section 2.2. Reducing the NMDA conductances in the simulations also enabled the effects of a reduction of acetylcholine in aging that operates by reducing synaptic modification during learning to be investigated (Section 2.5.2).

The protocol also enabled the effects of reduced acetylcholine in aging causing an increase of Ca\(^{2+}\) mediated afterhyperpolarization and thereby spike frequency adaptation to be investigated (Section 2.5.3), by enabling this mechanism in the simulations with different magnitudes corresponding to different reductions of acetylcholine.

4 Results

4.1 NMDA receptor hypofunction, and reduced synaptic strength

In integrate-and-fire simulations, the effect of reduction in the NMDA receptor activated channel conductances on the short-term memory performance of the integrate-and-fire network are shown in Fig. 3. This reduction was for all NMDA receptors in the network, i.e. those on the excitatory recurrent collateral connections within and between the different excitatory pools, and onto the inhibitory neurons. 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. It is clear that rather a small reduction in synaptic strength (caused e.g. by less efficacious LTP), or in the NMDA receptor conductance, of 5%, causes a major reduction in the percentage of trials on which the short-term memory is maintained. The reduction also, understandably, 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 Fig. 4 for the condition in which NMDA conductance is reduced by 5%. This reduction of the firing rate decreases the depth of the basin of attraction of 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 (Rolls 2008a, Rolls and Deco 2010, Rolls 2014a). The noise acts to probabilistically knock the firing out of its attractor state during the short-term memory period of 3–5 s in these simulations.

Further evidence on the reduction of firing rates during the memory period produced by NMDA receptor hypofunction is shown in Fig. 5. The firing rates were measured across all the neurons in pool S1 during the memory period on correct trials only, after the cue had been removed, during the time period in the simulations of 4–5 s. (For the reduction of NMDA receptor activated synaptic conductance of 10%, there were no trials on which the
memory was correctly maintained during this period, and the rates reflect a value close to the spontaneous firing rate before the memory retrieval cue was applied.) It is clear that the firing rates during the memory period are considerably reduced by the reductions in NMDA-mediated synaptic transmission. This means that the depth of the basins of attraction is being reduced by the reduction in synaptic transmission, and this is relevant to the resistance of the attractor short-term memory state to disruption by the spiking-related noise.

The reduction in firing rate is also relevant to any effects produced in a particular neuronal population, and could be reflected for example in hypoemotionality due to reduced firing in emotion-related states elicited by reward and non-reward in the orbitofrontal and anterior cingulate cortex (Rolls 2014a).

4.2 Effects of spike frequency adaptation mediated by a reduction in acetylcholine

Fig. 6 shows the effects of different increases in $g_{\text{AHP}}$ to simulate the effects of different reductions of acetylcholine in normal aging. It is shown (top) that the persistence of short-term memory is markedly reduced as acetylcholine is reduced. It is also shown (bottom) that as acetylcholine is reduced (i.e. as $g_{\text{AHP}}$ increases), that the spontaneous firing rate state becomes a little less stable. Fig. 4 further shows that the effect of a reduction in acetylcholine that produces an increase in the Ca$^{2+}$ mediated potassium-dependent after-hyperpolarization mechanisms that produces spike-frequency firing rate adaptation is to decrease the firing rates of the short-term memory pool. This decrease is seen both during the delivery of the short-term memory cue (1–3 s in Fig. 4), and during the short-term memory period after the cue has been removed (3–5 s in Fig. 4). 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 gradually reducing firing rate in the period of 1.0–1.5s shows the firing rate adaptation, which has a similar time course to that which we have recorded in single neurons in the inferior temporal visual cortex of the awake behaving macaque (Tovee et al. 1993). Also of interest is that after the cue is removed from pool S1 at time=3 s, the neurons decrease their firing rates for several hundred ms, 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 will help to reduce the reduction in the short-term memory performance of attractor networks involved in short-term memory and attention that may occur in aging.

4.3 Reduced GABA function when NMDA receptor functionality is reduced

The results in Fig. 3 show that when NMDA functionality, glutamate transmission, or excitatory synaptic strength, are reduced, short-term memory is impaired on many trials because the reduced firing rates and depth of the basins of attraction cause the firing of the cued attractor to fail to be maintained, and 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 is shown in Fig. 7 that a reduction by 10% in the GABA synaptic conductance can at least partially help the memory to be maintained. In the upper part of the Figure this is shown by the dotted plot, which may be compared with the effects shown without any reduction of GABA by the plot with the solid line.

However, the effects of the reduction of GABA to help maintain a cued high firing rate attractor short-term memory state come at a cost, as shown in the lower part of Fig. 7. This shows 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. 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, because of the risk of the spontaneous firing rate state when no stimuli are applied becoming unstable. This would increase the risk for example of hallucinations or epilepsy.

Given that an effect of a reduction in acetylcholine can have an effect of reducing inhibitory GABA transmission (Giocomo and Hasselmo 2007, Deco and Thiele 2011), the results of the reduction of GABA synaptic conductance by 10% shown in Fig. 7 when the NMDA conductance is normal (0% reduction) is interesting. The lower part of the Figure shows that the GABA reduction impairs the stability of the spontaneous firing rate state, i.e. when no cues are applied. This type of alteration of instability is not a feature of the reduction of acetylcholine, and thus this particular effect of acetylcholine may be minor in terms of its effect on cortical networks relative to the effects of reduced acetylcholine in reducing the stability of the high firing rate state that maintains the short-term memory which are described in sections 4.1 and 4.2.

5 Discussion

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. We do note at the outset though that the purpose of this paper is to illustrate this computational neuroscience approach to understanding how neurobiological changes with normal aging may influence cognitive and especially memory functions, rather than to simulate here the effects of all the possibly relevant neurobiological changes. The aim is to describe a framework, which can be developed further to incorporate new neurobiological findings into new synaptic and biophysical mechanisms that are modelled.

First, the stability of short-term memory networks would be impaired, and it might be difficult to hold items in short-term memory for long, as the noise might push the network easily 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, and very interestingly, 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 Fig. 4.

Third, the recall of information from episodic memory systems in the temporal lobe involved for example in object-place memory (Rolls 2008a, Dere et al. 2008, Rolls 2008b, Rolls 2010) would be impaired. This would arise because the positive feedback from the recur-
rent collateral synapses that helps the system to fall into a basin of attraction (Deco and Rolls 2006), representing in this case the recalled memory, would be less effective, and so the recall process would be more noisy overall, and in particular would not be maintained for several seconds while the recalled memory is 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 (Rolls 2008a, Rolls 2010), 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 (Rolls 2014a, Rolls and Grabenhorst 2008, Grabenhorst and Rolls 2011, Rolls 2014a), in which there would be a reduction in firing rate due to the NMDA receptor hypofunction.

Although NMDA hypofunction may contribute to cognitive effects such as poor short-term memory and attention in aging and in schizophrenia, the two states are clearly very different. Part of the difference lies in the positive symptoms of schizophrenia (the psychotic symptoms, such as thought disorder, delusions, and hallucinations) which may be related to the additional downregulation of GABA in the temporal lobes, which would promote too little stability of the spontaneous firing rate state of temporal lobe attractor networks, so that the networks would have too great a tendency to enter states even in the absence of inputs, and to not be controlled normally by input signals (Loh, Rolls and Deco 2007a, Loh, Rolls and Deco 2007b, Rolls, Loh, Deco and Winterer 2008b, Rolls and Deco 2010, Rolls 2014a). However, in relation to the cognitive symptoms of schizophrenia, there has always been the fact that schizophrenia is a condition that often has its onset in the late teens or twenties, and we suggest that there could be a link here to changes in NMDA and related receptor functions that are related to aging. In particular, short-term memory is at its peak when young, and it may be the case that by the late teens or early twenties NMDA and related receptor systems (including dopamine) may be less efficacious than when younger, and the excitatory input to neurons may be reduced because of the decrease in spine density (Glausier and Lewis 2013), so that the cognitive symptoms of schizophrenia are more likely to occur at this age than earlier (Rolls and Deco 2011).

It is clear that the firing rates during the memory period are considerably reduced by the reductions in NMDA-mediated synaptic transmission, as shown in Figs. 4 and 5. This means that the depth of the basins of attraction (see Equation 1) is being reduced by the reduction in synaptic transmission, and this is relevant to the resistance of the attractor short-term memory state to disruption by the spiking-related noise. Consistent with these findings from computational neuroscience, blockade of NMDA transmission in the macaque dorsolateral prefrontal cortex does impair short-term memory related persistent neuronal firing in the dorsolateral prefrontal cortex, and indeed this effect is greater than that produced by blockade of AMPA receptors (Wang et al. 2013). Moreover, acetylcholine acting through nicotinic α7 receptors facilitates this NMDA effect (Yang, Paspalas, Jin, Picciotto, Arnsten and Wang 2013). The reduction in firing rate is also relevant to any effects produced in a particular neuronal population, and could be reflected for example in hypoemotionality due to reduced firing in emotion-related states elicited by reward and non-reward in the orbitofrontal and anterior cingulate cortex (Rolls 2014a).

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, as shown in Fig. 7. The effect of the spontaneous firing rate state when no stimuli are applied becoming unstable 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, this approach suggests that a better approach would be to try for treatments that would increase the excitatory glutamatergic transmission in cortical networks. This could involve effects such as that of glycine in modulating upwards the NMDA receptor (Lin, Lane and Tsai 2012); or agents such as AMPAkinines that increase transmission through effects on the AMPA glutamatergic receptors (Lin et al. 2012); or agents that mimic dopaminergic or cholinergic effects; or other types of stimulant 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 of aging. Indeed, 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 find 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 (Zurkovsky, Taylor and Newhouse 2013, Levin 2013), both of which are predicted from the effects described here of acetylcholine on the stability of memory networks in the prefrontal cortex and hippocampus, and on the firing rates of neurons in areas such as the orbitofrontal and anterior cingulate cortex involved in emotion and mood. Finally, although the research described here has focussed on the 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 (Hu, Ondrejcak and Rowan 2012).

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Figure 1: The attractor network model. The excitatory neurons are divided into two selective pools S1 and S2 (with 80 neurons each) with strong intra-pool connection strengths $w_+$ and one non-selective pool (NS) (with 640 neurons). The other connection strengths are 1 or weak $w_-$. The network contains 1000 neurons, of which 800 are in the excitatory pools and 200 are in the inhibitory pool IH. The network also receives inputs from 800 external neurons, and these neurons increase their firing rates to apply a stimulus to one of the pools S1 or S2. The Supplementary Material contains the synaptic connection matrices.
Figure 2: Experimental protocol, and classification of trial types. The spontaneous period was from 0–1 s with no memory cue applied. The memory cue was applied for the period 1–3 s. For the period 3–5 s the cue was no longer present, and the maintenance of a correct retrieved memory was measured as reflected in a continuing high firing rate of the cued neuronal pool, S1. The firing rates on a single trial for the 80 neurons in pool S1 are shown for 3 types of trial. Top. A correct trial showing baseline performance. Middle. A trial on which the short-term memory failed after the cue was removed, and the firing rate fell back to the spontaneous firing rate. Bottom. A trial on which the firing was unstable in the spontaneous firing rate period from 0–1 s, with the rate increasing even with no memory cue yet applied.
Figure 3: Effects of reductions of NMDA receptor conductance on short-term memory in the integrate-and-fire network. Top. 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 S1 that was > 10 spikes/s higher at the end of the delay period than for the uncued pool S2. Bottom. The percentage of trials on which the spontaneous firing rate state was stable (with a firing rate of < 10 spikes/s) 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 1000 trials.
Figure 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. Timecourse: 0–1 s is spontaneous activity; 1–3 s is when the short term memory cue is applied to neuron pool S1; 3–5 s is the period after the cue is removed when 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/s more than in pool 2) 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 non-specific pool. Inhib: the pool of inhibitory neurons.
Figure 5: Effects of reductions of NMDA receptor conductance on the firing rates of neurons in the short-term memory integrate-and-fire network during the short-term memory period of 4–5 s in the simulations. The firing rates are shown for correct trials only, 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/s more than in pool 2) until the end of the trial. (For the reduction of NMDA receptor activated synaptic conductance of 10%, there were no trials on which the memory was correctly maintained during this period, and the rates reflect a value close to the spontaneous firing rate before the memory retrieval cue was applied.)
Figure 6: Effects of spike frequency adaptation mediated by a reduction in acetylcholine on short-term memory. Top. The effects of different increases in the conductance of Ca$^{2+}$ channels (abscissa) caused by reduction of acetylcholine 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 S1 that was $> 10$ spikes/s higher at the end of the delay period than for the uncued pool S2. Bottom. The percentage of trials on which the spontaneous firing rate state was stable (with a firing rate of $< 10$ spikes/s) at the end of the 1 s spontaneous firing rate period before a short-term memory cue was applied to pool S1.
Figure 7: Effects of reductions of NMDA receptor conductance on short-term memory in the integrate-and-fire network without (NMDA) and with (NMDA + GABA -10%) a 10% reduction in GABA synaptic transmission. Top. 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 S1 that was > 10 spikes/s higher at the end of the delay period than for the uncued pool S2. Bottom. The percentage of trials on which the spontaneous firing rate state was stable (with a firing rate of < 10 spikes/s) 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.