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Functional role of entorhinal cortex in working memory processing

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Abstract

Our learning and memory system has the challenge to work in a world where items to learn are dispersed in space and time. From the information extracted by the perceptual systems, the learning system must select and combine information. Both these operations may require a temporary storage where significance and correlations could be assessed. This work builds on the common hypothesis that hippocampus and subicular, entorhinal and parahippocampal/postrhinal areas are essential for the above-mentioned functions. We bring up two examples of models; the first one is modeling of in vivo and in vitro data from entorhinal cortex layer II of delayed match-to-sample working memory experiments, the second one studying mechanisms in theta rhythmicity in EC. In both cases, we discuss how cationic currents might be involved and relate their kinetics and pharmacology to behavioral and cellular experimental results.

Keywords: Working memory; Delay match-to-sample; Theta oscillations; Biophysical modeling

1. Introduction

1.1. Background

The entorhinal cortex (EC) is very important as it is positioned as a 'gateway' between neocortical association areas and the hippocampal system (Fig. A.1). It has been suggested to work as a temporal buffer of incoming information for hippocampus (Hasselmo, Fransén, Dickson, & Alonso, 2000). Entorhinal cortex is indeed involved in working memory for novel (Stern, Sherman, Kirchhoff, & Hasselmo, 2001) as well as specific attributes of items (Otto & Eichenbaum, 1992). Hippocampus itself has been suggested to be involved in associating information for declarative memory (Eichenbaum, 2000). It is for instance found to be crucial for solving the transitive inference task (Dusek & Eichenbaum, 1997). Anatomically, the superficial layers of EC receives the input from neocortex and provides the main input via the perforant path to the dentate gyrus of the hippocampal formation. The deeper layers receive input mainly back from hippocampus field CA1 and the subiculum and provide the output back to the neocortical areas. The deeper layers also project to the more superficial layers, creating a loop through the entorhinal-hippocampal system. Sensory, motor and associational information is thereby processed in EC and hippocampus before being stored permanently in neocortex.

In this presentation, we will give two examples of our modeling of EC function. One will be concerned with working memory (Fransén, Alonso, & Hasselmo, 2002) and the other with generation of theta rhythmicity (Fransén, Alonso, Dickson, Magistretti, & Hasselmo, 2004). In both models, a cationic current plays a central role.

1.2. Theta oscillations

A prominent physiological characteristic of the hippocampal system is the 4–12 Hz theta oscillations (Buzsaki, 2002). Behaviorally, theta amplitudes correlate with human working and declarative memory performance (Bastiaansen & Hagoort, 2003) and cognitive load (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999) as well as learning in rodents (Griffin, Asaka, Darling, & Berry, 2004; Hasselmo, Bodelon, & Wyble, 2002a; Hasselmo, Hay, Ilyn, & Gorchetchnikov, 2002b; Olvera-Cortes, Guevara, &

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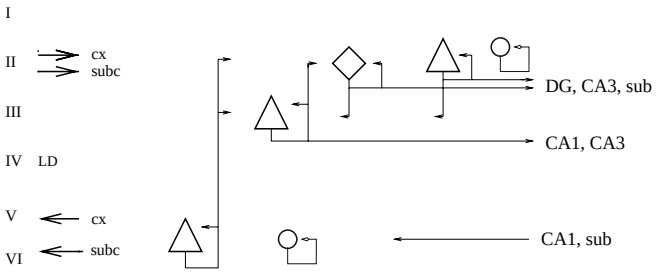

Fig. A1. Entorhinal cortex structure. cx neocortical pyramidal cell afference or efference, subc subcortical region, LD lamina dissecans (a cell body free layer), DG dentate gyrus, CA3 and CA1 hippocampal subdivisions, sub subiculum. Pyramidal cells are symbolized by triangles, stellate cells by rectangles and inhibitory interneurons by circles.

Gonzalez-Burgos, 2004; Winson, 1978). Further, both amplitude and phase are correlated with performance in sensory-motor discrimination (Kay, 2005) and working memory processing in the rat (Kay, 2005; Lee, Simpson, Logothetis, & Rainer, 2005). Sources of this rhythm include brain stem activating system, basal forebrain, cortex and hippocampal regions. In parallel with rhythmic input, local networks in these regions, as well as neurons in these networks, may possess intrinsic resonant properties. One part of this theta network is the projection from neurons in the medial septum-diagonal band of Broca to entorhinal cortex. As discussed above, entorhinal cortex is important in relation to learning and memory as it provides the main input to hippocampus. In the EC slice preparation, administration of the cholinergic agonist carbachol leads to theta-like network rhythmicity (Dickson & Alonso, 1997). We have investigated mechanisms involved in the generation of theta rhythmicity. More specifically, we have studied the subthreshold membrane potential oscillations displayed by the main principal cell type of layer II, the stellate cell (Fransén et al., 2004). Moreover, as will be shown in this work, intrinsic rhythmicity enables a network of stellate cells to fire at theta frequency.

1.3. Working memory

Working memory (WM) is a non-permanent memory, sometimes also referred to as short-term memory (Baddley, 1986). Based on findings in psychological memory research, working memory is assumed to depend on continuous activation. It is classified as explicit and relying on self-consciousness. Most studies of the physiological basis of working memory have been done in prefrontal cortex (PFC) of primates performing a so-called delayed match-to-sample (DMS) paradigm (Fuster, 1995; Goldman-Rakic, 1995). In this type of experiment, a sample stimulus and a test stimulus are separated by a delay. After the presentation of the test, a choice in behavior has to be done to signify whether the two stimuli were identical (a match) or not (a non-match). Working memory is assumed to be needed to still remember the sample when the test is presented after the delay.

Single cell activity in areas outside the frontal lobe has also been related to working memory, e.g. the inferotemporal (IT), parietal (PP) and entorhinal (EC) cortices. In the entorhinal cortex, cells are found which show activity related to the main behavioral components of the working memory task (Eichenbaum, Otto, & Cohen, 1994; Young, Otto, Fox, & Eichenbaum, 1997). Furthermore, entorhinal and perirhinal cortex ablations impair performance in delayed match-to-sample tasks. In a study of Otto et al. (1992) the similarities and differences between the experiments and results on the two areas PFC and EC are discussed. One conclusion is that while PFC seems to be involved in the general rules of the task, the EC is involved in the representation and processing of specific individual items. Furthermore, there are also indications that EC might be specifically involved in the representation of novel objects (McGaughy, Jindal, Eichenbaum, & Hasselmo, 2003; Stern et al., 2001).

1.4. Acetylcholine and EC

Cholinergic modulation in the entorhinal cortex may be particularly important for performance in delayed match-to-sample tasks. Systemic injections of muscarinic cholinergic antagonists have been shown to impair performance on recognition memory tasks, while sparing performance at zero second delays (Bartus & Johnson, 1976; Penetar & McDonough, 1983). This occurs with both the antagonists scopolamine and atropine. The locus of cholinergic effect has been tested with localized injection of cholinergic antagonists in monkeys. Tang, Mishkin, and Aigner (1997) demonstrated that infusion of scopolamine into perirhinal cortex, with a very likely spread into entorhinal cortex, impairs performance on a recognition memory task, whereas infusion into adjacent structures did not cause impaired performance. Also, injections of scopolamine appear to impair the encoding of new stimuli for recognition, observed with local infusion of scopolamine (Tang et al., 1997) or with systemic injections of scopolamine in monkeys (Aigner & Mishkin, 1986; Aigner, Walker, & Mishkin, 1991) and human subjects (Ghonheim & Mewaldt, 1975; Peterson, 1977). Thus, in addition to a role in short-term memory

function, sustained activity in entorhinal cortex could also be very important for effective encoding of long-term representations through synaptic modification in the hippocampal formation. As mentioned in the section on theta above, cholinergic agoniststs produce theta-like rhythmicity in the EC slice and long-term memory impairments could thus be due to interference with theta generation (Bunce, Sabolek, & Chrobak, 2004).

1.5. Clinical aspects

The EC is also important from a clinical perspective. One of the major forms of epilepsy involves the medial temporal lobe, and the EC and hippocampus have been pointed out as starting points of seizure activity. Activation of cationic currents, like the calcium activated NCM-current we will discuss below, could due to its depolarizing nature contribute to neuronal excitability, and thereby be involved in epilepic activity. Further, in Alzheimer's disease, the first region to show signs of change is the EC. In the treatment, agents that elevate endogeneous acetylcholine (acetylcholinesterase inhibitors) are used, and one target may be the cholinergically activated cationic channel studied in this project.

2. Methods

Models on working memory have to a large extent been focused on PFC (Amit & Brunel, 1997; Durstewitz, Seamans, & Sejnowski, 2000; Lisman & Idiart, 1995), but there is also some modeling work on IT, e.g. Jensen, Idiart, and Lisman (1996), Sohal and Hasselmo (2000). Common to all models is the assumption that the experimentally observed persistently active cells are a necessary component in the working memory function. In most models, the recurrent connectivity of the network is enabling a cell population to be persistently active. Other models, including the present one, obtain persistent rates by intrinsic cellular properties providing the cell with bi- or multistable firing properties. In EC, there are some modeling studies on the cellular level (Fransén et al., 2002; White, Budde, & Kay, 1995) and network level (Fransén et al., 2002; Hasselmo et al., 2000).

There are several modeling studies concerned with the generation of theta e.g. (Gillies, Traub, LeBeau, Davies, Gloveli and Buhl, 2002; Hajos, Hoffmann, Orban, Kiss, & Erdi, 2004; Jensen & Lisman, 1996; Rotstein et al., 2005; Tiesinga, Fellous, Jose, & Sejnowski, 2001; CA3, CA1, Yamaguchi, Aota, Sato, Wagatsuma, & Wu, 2004). Some work has focused on studies of specific subfields of hippocampus (Gillies et al., 2002; Rotstein et al., 2005; Tiesinga et al., 2001), whereas other studies the septo-hippocampal interaction (Hajos et al., 2004). In some work the mechanism is based on a cellular property, i.e. AHP (Jensen & Lisman, 1996) or membrane potential oscillation (Rotstein et al., 2005; Tiesinga et al., 2001) but in most studies a synaptic mechanism is the main factor (Gillies et al., 2002; Hajos et al., 2004; Jensen & Lisman, 1996; Rotstein et al., 2005; Yamaguchi et al., 2004). In some of these studies specific attention is put on the synchronization in the neural population (Rotstein et al., 2005; Yamaguchi et al., 2004).

In this work, biophysical simulations were developed using the GENESIS simulation package. The method for numerical solution to differential equations was the modified Crank-Nicholson by Michael Hines. Time steps of 50–150 μs were used for the simulations. Neurons were simulated with a compartmental model of entorhinal cortex layer II cells (Fransén et al., 2002, 2004). Further details of the model can be found in the appendix 'Brief summary of model'.

3. Results

3.1. Simulating delayed match-to-sample experiments

Data from Alonso's lab (Klink & Alonso, 1997; Shalinsky, Magistretti, Ma, & Alonso, 2002) has shown that the cholinergic agonist carbachol affects a non-specific calcium-sensitive cationic current (I_{NCM}). In a project this current and its effects on cellular properties of the pyramidal type cell of layer II has been studied (Fransén et al., 2002). When the effects of carbachol are simulated, a depolarizing plateau potential appears. Calcium influx through high-threshold calcium channels during spikes activates I_{NCM}, and this elicits further depolarization, resulting in persistent activity (the plateau potential). Modulatory activation may thus affect the excitability of the cells and thereby enable persistent activity and thereby support working memory.

As discussed above, the plateau potentials may produce spiking activity that could be related to the enhanced delay period spiking in a match-to-sample experiment. Furthermore, even without persistent spiking activity, the changes in I_{NCM} could mediate memory type function. Simulations demonstrate that in control conditions, a weak synaptic input following a spike does not elicit additional spiking activity, whereas after cholinergic enhancement of I_{NCM}, the same magnitude of synaptic input elicits additional spiking activity. This type of response could mediate recognition of matching stimuli in a DMS or recognition task. Further, in a local network, the contribution to match suppression from IPSPs evoked by lateral inhibition was studied.

To sum up, the single cell simulations have demonstrated that: (1) The muscarinic activation of the calcium-sensitive component of the non-specific cation current I_{NCM} could underlie the plateau potentials and bursting activity observed in pyramidal cells in slice preparations of entorhinal cortex. (2) Single cell properties due to the cholinergically activated I_{NCM} could contribute to

the maintenance of delay activity and match enhancement in working memory delayed match-to-sample tasks (DMS) or non-match tasks (DNMS). (3) Working memory can be maintained in the presence of a limited number of distractors. The effect of these may be an inhibitory (hyperpolarizing) effect on the activity from the sample stimulus. Tolerance to distractors may be explained by the independence of I_{NCM} of voltage.

Subsequently, a network of cells representing layer II was studied. Network models of stellate, pyramidal-like and interneurons in layer II of the rat entorhinal cortex (Fig. A.1) were used to explore cellular and network components involved in neuronal responses to stimuli during the working memory delayed match-to-sample task. In layer II network simulations, cellular response properties arose naturally from the randomly connected network, without any procedure focused on tuning of synaptic connections, suggesting that a network with the intrinsic phenomena described here easily manifests the various response properties described in unit recording from behaving animals. Fig. A.2 describes the network connectivity representing EC layer II. The main cell types are represented together with input from a neocortical origin. The proportions of cells correspond to those found in layer II. An input pattern is represented by activating a third of the input cells. As connectivity is limited within a local neighborhood, some cells become input selective whereas others become input non-selective. Local connectivity and selective/non-selective cells were shown, together with intrinsic cellular memory from the cationic current, to be sufficient to generate a range of experimentally observed neuronal response types.

Fig. A.3 shows examples of activity in the network during a matching trial (repeated activation of input neurons). This results in a diverse range of firing patterns during this match trial. Fig. A.4 shows activity in the network during a non-match trial. One population of neurons primarily receive connections from one set of input neurons, whereas another population of neurons primarily receive connections from another set of input neurons, but the random overlap of input and connectivity between these two populations of neurons

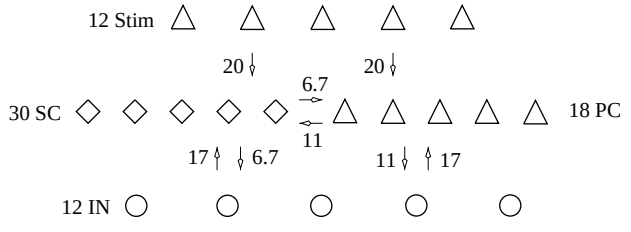

Fig. A2. Network connectivity representing EC layer II together with its neocortical input. Cell symbols as in Fig. A.1. Cells were connected locally, and numbers beside arrow indicate percent connections used out of all possible connections between two populations. Stim, neocortical input cells representing three different inputs. SC, stellate cells; PC pyramidal cells; IN, inhibitory interneurons. Numbers besides abbreviation indicate number of cells simulated.

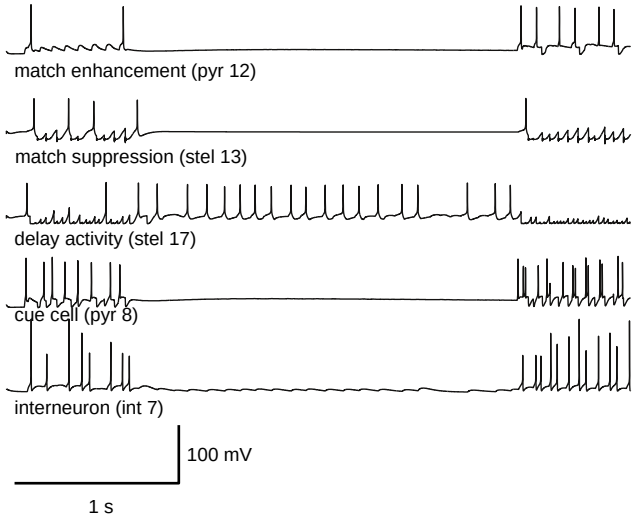

Fig. A3. Examples of individual neuronal responses in the network shown in Fig. A.2 during a match trial, i.e. the same input given for both sample and test. From top to bottom: match enhancement, match suppression, pure delay activity, and pure cue activity. For almost all simulations, all these cell types were represented.

allows interactions resulting in non-match phenomena. Thus, the network simulations presented above demonstrate that network interactions between cells could underlie additional phenomena observed in DMS tasks. These phenomena include: (1) Match suppression, which could result from inhibition of neurons by other neurons undergoing match enhancement. (2) Non-match enhancement, which could result from strong excitatory input from non-selective cells. (3) Non-match suppression, which could result from greater activation of inhibitory interneurons by

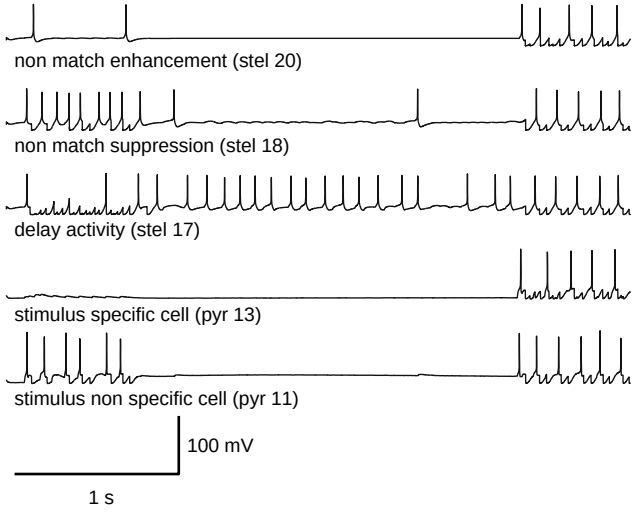

Fig. A4. Examples of individual neuronal responses in the network during a non-match trial. The inputs given for sample and test are different but have a partial overlap i.e. partly activating the same population and partly different cell populations. From top to bottom: non-match enhancement, non-match suppression, delay activity, pattern specificity and pattern non-specificity. For almost all simulations, all these cell types were represented.

non-selective cells. (4) An explanation for the role of the non-selective cells. In the non-match simulations, the differential action of the selective and the non-selective cells and their connectivity to interneurons provide a mechanism for causing non-match enhancement and suppression activity.

After the presentation of our model, several lines of evidence in favor of it have been presented. Regarding the cholingergic component of working memory, both selective lesions of cholinergic input to EC (Turchi, Saunders, & Mishkin, 2005) as well as cholingergic deafferentiation of EC (McGaughy et al., 2003) caused impairments in a working memory task. Further, we have previously shown that the current NCM is M1 activated (Klink & Alonso, 1997). In a muscarinic M1 null knockout, severe impairments were observed for a working memory task (Anagnostaras, Murphy, Hamilton, Mitchell, Rahnama and Nathanson, 2003).

3.2. Simulating subthreshold oscillations

Work within this project (Dickson, Magistretti, Shalinsky, Fransén, Hasselmo and Alonso, 2000; Fransén et al., 2004) has shown that subthreshold cellular properties of EC neurons could underlie theta rhythmicity. Within the project, a kinematic analysis and biophysical model of the hyperpolarization activated non-specific cationic current I_h has been done (Fransén et al., 2004). Experimental data (Dickson et al., 2000) has shown that this current together with a persistent type sodium current I_{NaP} are responsible for the subthreshold oscillations of the EC stellate cells, the principal cell type in layer II. These oscillations, as described in the introduction, are believed to play an important role in the generation of the septo-hippocampal theta rhythm.

The model of I_h has been used in a compartmental biophysical model of a stellate cell, including several other ionic currents. Simulations have shown that I_h and I_{NaP} are a sufficient condition for generating the subthreshold oscillations (Fig. A.5). The pharmacological effects of cesium, barium and ZD7288 have been successfully replicated. Further, the model also replicates the spike clustering seen in these neurons (Fig. A.6). Consistent with experiments, these clusters depend mainly on a calcium dependent mechanism, in the model a calcium dependent potassium current. Experiments however also show a weak calcium independent component. Based on the modeling, we propose that this could be caused by the slow component of I_h.

A recent experimental study from the Kandel laboratory (Nolan, Santoro, Morozov, Siegelbaum, & Kandel, 2003) explored effects of knocking out the HCN1 gene (coding an h-channel). The results of this study support several conclusions of our model. The HCN-current studied had a biphasic kinetics as the h-current in our study. In the knockout, and as predicted by our model, sag was absent, as was subthreshold oscillations, and most interestingly spike

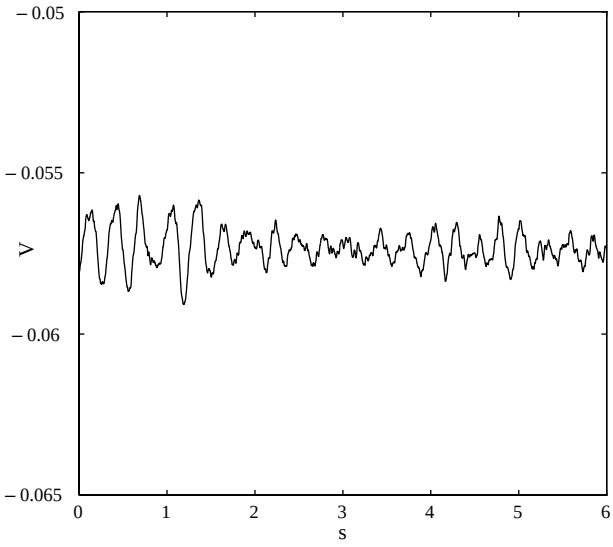

Fig. A5. Membrane potential oscillations. The figure displays the soma membrane potential during a depolarizing current injection which depolarized the cell from resting level at −63 to −57 mV. Membrane potential oscillations depend on an interplay between the persistent sodium current and the hyperpolarization activated cationic current I_h.

clustering was affected. Further, a possible contribution to the mAHP by the h-current as proposed in our study has recently been shown in CA1 pyramidal neurons (Gu, Vervaeke, Hu, & Storm, 2005).

Recently, the single cell model of h-current effects has been extended to investigate the effects of these intrinsic subthreshold oscillations of the stellate cells on spiking activity in a network of stellate cells. Simulations show that theta frequency firing can be produced in the network (Fig. A.7). The figure shows a network of 12 stellate cells. Cellular intrinsic subthreshold oscillations provide

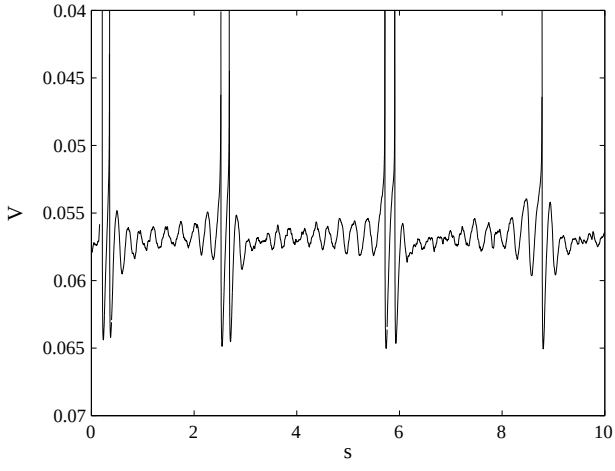

Fig. A6. Spike clustering. The figure shows the typical clustered spike pattern of stellate cells. Doublets and single spiking is mixed with membrane potential oscillations. Clustering in the model depends mainly on AHP buildup from a Ca-dependent potassium current, but also to a smaller extent on the deactivation of the h-current.

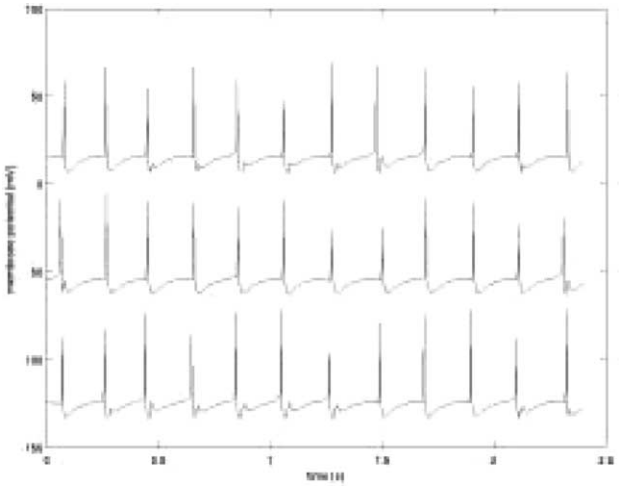

Fig. A7. Theta rhythmic firing in a network. Generation of theta rhythmic firing in a EC layer II stellate neuron network. Three cells are shown out of 12 simulated cells. Connectivity is sparse, 17%, and is composed of both kainate/AMPA and NMDA type components. The cell type used displays intrinsic subthreshold oscillations, which provides a subthreshold resonance in the theta frequency range. Model neurons are depolarized by a noisy current injection up to spiking. Cell firing is synchronized due to synaptic coupling between neurons.

a subthreshold resonance in the theta frequency range. Connectivity is sparse, 17%, and is composed of both kainate/AMPA and NMDA type components. Cells are synchronized by a combination of cellular properties, i.e. subthreshold resonance, and type of synaptic coupling, i.e. excitatory with a fast component. It is therefore possible that the cationic current I_h takes part in the generation of EC theta rhythmicity. It seems that similar mechanisms are present also in hippocampus, as pyramidal cells of CA1 show a resonance due to an interplay between an h-current, an M-type potassium current and a persistent sodium current (Hu, Vervaeke, & Storm, 2002). Robust rhythmicity in the hippocampal region may therefore be a product of cellular and network properties working in concert.

4. Discussion

Work presented here analyses the potential role of entorhinal cortex in working memory processing and studies mechanisms in generation of theta rhythmicity. While it is clear that amplitude as well as phase relationship of neuronal theta activity correlates with behavioral performance (Kahana et al., 1999; Kay, 2005; Olvera-Cortes et al., 2004), the functional role of this in information processing remains open. Based on modeling work, a multitude of hypothesis have been suggested, e.g. (Hasselmo, 1995; Levy, 1996; O'Reilly & McClelland, 1994; Rolls, 1996; Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996), and more recently by i.e. Hasselmo et al. (2002a), Hasselmo et al. (2002b), Rolls, Xiang, & Franco, 2005 and Yamagushi et al., 2004.

On the basis of lesions and imaging studies, it has been suggested that while working memory operations in prefrontal cortex may be important for monitoring familiar stimuli, the medial temporal lobe may be more important for matching and maintenance of novel stimuli (Stern et al., 2001). The cellular mechanisms studied in this project might be particularly important for representations of novel stimuli, for which learning by synaptic modifications has not yet occurred. The delay activity during working memory processing might also be important for subsequent memory consolidation (Schön, Hasselmo, Lopresti, Tricarico, & Stern, 2004).

As discussed in the introduction, the theta rhythm may reflect interactions within and between neocortex and the hippocampal system for memory formation and retrieval (Bastiaansen & Hagoort, 2003). However, theta is also involved in working memory processing (Bunce et al., 2004; Kay, 2005; Lee et al., 2005). For instance, a significant enhancement in theta band energy was found during the delay period of a visual working memory task (Lee et al., 2005). Importantly, they were able to correlate single neuron activities with theta as measured by local field potentials. In 90% of the neurons, action potential timing varied systematically with LFP theta phase angle. Furthermore, in a different study by Bunce et al. (2004) of a delayed non-match-to-sample radial maze task, post-acquisition intraseptal cholinergic treatment disrupted retention 2 h later possibly by interfering with theta dependent memory consolidation. Theta may thus be linking working memory and long term memory processing.

We have in this article reviewed our work concerning the possible involvement of two different cationic currents in the processing mentioned above. Even though this processing may build on functions of macroscopic networks (theta oscillations and delay activity), these functions must be subserved and implemented by the underlying elements; organelles, intracellular biochemical networks, ion channels etc. Activation of channels produces a change of characteristics of the cell. As the cell changes, the network it forms part of also changes, molecular events thereby eventually leading to behavioral consequences.

Appendix A. A Brief summary of model

A.1. Stellate cell model

In the simulations of generation of subthreshold membrane potential oscillations, the entorhinal cortex layer II stellate cell (Klink & Alonso, 1997c) was reduced to an equivalent cylinder model composed of seven compartments. One compartment represented the soma, one compartment represented the initial segment, three compartments connected in succession represented the primary, secondary and tertiary segments of a single principal dendrite (to provide appropriate dendritic

attenuation for synaptic inputs to the cell), and two connected compartments represent all remaining dendrites lumped together to constitute the main 'load' to the soma. The proximal of the principal compartments and the proximal of the lump compartments and the initial segment are all connected to the soma. The lengths and cross sections of the three principal dendrite compartments were adjusted to give the dendrite a length constant of two (sealed-end condition). Further, resting membrane potential, input resistance, and membrane time constant were adjusted to comply with this experimental data.

To study the generation of membrane potential oscillations, a minimal model containing only the two currents, a persistent sodium current and a hyperpolarization activated cationic current, hypothesized to generate the oscillations were studied. To study the generation of oscillations under more realistic conditions, more ionic currents were subsequently included. The full cell model had in addition the Na^+ and K^+ currents responsible for fast action potentials, a high-threshold Ca^{2+} current, a calcium-dependent K^+ current, a fast calcium- and voltage-dependent K^+ current, and a non-specific Ca^{2+}-dependent cationic current. The channel models used Hodgkin–Huxley representations of intrinsic currents. Cell, ion channel equations and parameters can be found in Fransén et al. (2004).

A.2. Pyramidal cell model

The properties of entorhinal pyramidal cells were simulated with biophysical models containing six compartments, with an emphasis on the calcium-sensitive non-specific cation current I_{NCM}. The pyramidal cell is composed of six compartments, one representing the soma, three the apical dendrite, one a basal dendrite and one compartment representing all but one basal dendrite lumped together, analogously as for the stellate cell. The proximal of the apical compartments, the basal dendrite and the lump compartment are all connected to the soma. The lengths and cross sections of the three apical dendrite compartments were adjusted to give the dendrite a length constant of two (sealed-end condition). Simulations with just a soma compartment and its conductances showed that dendritic compartments were not necessary for obtaining robust spiking activity during delay periods in the cell. However, these dendritic compartments were important for matching a range of features in the data including spike shape, after-hyperpolarization shape and spike frequency accommodation, as well as providing a more realistic attenuation of excitatory synaptic input.

The pyramidal cell model includes the following membrane currents: the Na^+ and K^+ currents responsible for fast action potentials, a high-threshold Ca^{2+} current, a calcium-dependent K^+ current, a fast calcium- and voltage-dependent K^+ current, a potassium leak current, a persistent type Na^+ current, a non-inactivating muscarinic K^+ current, as well as the muscarinic activated, non-specific Ca^{2+}-sensitive cationic current I_{NCM} (NCM). The compartment where spikes are initiated, here the soma, has Na^+ and K^+ currents with faster kinetics (Na^+ (soma) and K^+ (soma)), based on previous work (Traub, Jefferys, Miles, Whittington, & Toth, 1994).

The key current type, a non-specific Ca^{2+}-dependent cationic current, was modeled according to the calcium-dependent K^+ current by Traub, Wong, Miles, and Michelson (1991). For the associated calcium, we used 1D diffusion models of the intracellular calcium (Traub et al., 1991). Time constants for the maximal conductances were adjusted to produce spiking frequencies similar to those observed during delay activity and during match enhancement in recordings of single units in awake rats performing a delayed non-match to sample task. Cell, ion channel equations and parameters can be found in Fransén et al. (2002).

A.3. Interneuron model

The interneuron is modeled to replicate the basic properties of a fast spiking non-adapting type cell. The interneuron is composed of six compartments, one representing the soma, three a principal dendrite, and two compartments representing all but one of the dendrites lumped together. The interneuron model does not have the separate initial segment compartment.

The interneuron model has the Na^+ and K^+ currents responsible for fast action potentials (Na and K_{dr}), a high-threshold Ca^{2+} current (Ca_L), a calcium-dependent K^+ current (K_{AHP}), and a potassium leak current (K (leak)). The AHP was set at very weak values, consistent with the absence of spike frequency accommodation in these neurons. The compartment where spikes are initiated had currents with faster kinetics, as for the pyramidal cell. Ion channel equations and parameters can be found in Fransén et al. (2002).

A.4. Modeling of synaptic interactions

Synaptic contacts on the cells were of either a mixed AMPA/kainate and NMDA type, or of a mixed $GABA_A$ and $GABA_B$ type. Synaptic conductances between neurons were modeled with an alpha function. For the NMDA current the conductance was multiplied with the magnesium block conductance described in previous work (Zador, Koch, & Brown, 1990).

The simulations included a conductance based noise source. This represents potential effects of channel noise or synaptic noise in actual neural function. The noise was generated from a Poisson process and was placed on the proximal lumped dendritic compartment.

Before determining the synaptic conductance values, the relative proportions of the various components were fixed according to experimental data: The NMDA component has

the same PSP height as AMPA at −72 mV. $GABA_A$ is 70% of $GABA_B$ at −66 mV.

The synaptic conductances were adjusted so that firing rates would resemble those observed in recordings of entorhinal units from rats performing a delayed non-match to sample task (Young et al., 1997) for the various parts of an experiment, i.e. sample, delay, test.

To demonstrate that these simple interactions could be easily obtained with connectivity chosen randomly within constraints on number, distribution and weight, several network simulations were developed. As shown in Fig. A.2, the network consists of one population of 12 input cells representing association cortices projecting into entorhinal cortex, one population of 30 stellate cells, one population of 18 pyramidal cells and one population of 12 interneurons. The relative proportion of EC cells was determined according to experimental findings (Alonso & Klink, 1993), though these estimates may be subject to differences in probability of sampling different types of neurons.

The input cells were divided into three equal groups representing three stimuli A, B, C. A did not overlap at all with B or C, but B and C had moderate overlap. The existence of a connection was determined randomly within a five cell wide window of possible connections. The connection strengths from one of the inputs to either the stellates or the pyramidal cells had a uniform value for a central set of connections and decreasing values for neurons at the sides of the central projection, to provide fully activated cells as well as weakly activated cells. The input cells contacted both stellates and pyramidal cells. As a control, the number of connections, window width, and conductance values, were varied to test the sensitivity of the model. Equations and parameters can be found in Fransén et al. (2002).

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