Predictive Information Processing in the Septal-Hippocampal Region and its Involvement in Learning and Memory

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Abstract

In this paper, we propose a model of predictive learning in the septal-hippocampal region of the brain. We suggest that this region plays a primary role in monitoring the stability of the sensory cues that an animal receives from the external world, in relation to its own internally generated knowledge of its location, direction of gaze, and direction of movement. Our predictive model of information processing is based on the synaptic potentiation of hippocampal pyramidal cells during temporally asymmetric pairing of EPSPs and back-propagating action potentials. The model demonstrates that such potentiation of the synapses that the mossy fibre projections from the dentate gyrus make with pyramidal cells in the CA3 region of the hippocampus can cause a gradual shift backward in time of the postsynaptic activity of the CA3 cells, thus making their activity predictive of the upcoming sensory state of the animal. This is predictive activity has been observed experimentally in the firing of "place" cells in rat hippocampus, which corresponds initially to the rat being in a particular location. After repetitive experience, these cells begin to fire before the rat reaches this location, causing an apparent backward shift in space of the "place" field of the cell. The model offers both an explanation of this phenomenon, and more generally, a possible basis for further understanding of the role of the septal-hippocampal region in learning and memory.

Introduction

For some time one of our working hypotheses for the development of a biologically inspired computational model of learning and memory has been that the septal-hippocampal region in the mammalian brain plays a primary role in monitoring the stability of sensory cues the animal receives from the external world, in relation to its own internally generated knowledge of its location, direction of gaze, and direction of movement. (Denham and McCabe, 1996; Borisyuk et al, 1999). This process then provides other brain regions with the knowledge of what is stable and what is unstable in order to initiate appropriate activity in these regions, e.g. the consolidation of learning of stable sensory associations; the initiation of the learning of new associations in a novel or changed environment; and the initiation or inhibition of appropriate or inappropriate motor activity.

We postulate that the septal-hippocampal region carries out this function by learning from experience to use the current sensory context to predict the next sensory state in an episodic sequence of states, possibly as a consequence of its actions, i.e. a particular movement in a particular direction. The aim of forming such a prediction would be to detect when there was a change in sensory input that is inconsistent with prior experience. In this way it is able to discriminate between stable and unstable aspects of its environment, and in particular when it is in a completely novel environment.

We also propose that the feedback connections between the medial septum and the hippocampus plays a primary role in the dynamic, novelty-related control of the septal-hippocampal learning/recall process, and that the prefrontal region of neocortex plays a primary role in providing high-level (in a cognitive sense) goal and motivational state related modulation of this control mechanism. Our hypothesis is that the two main sub-regions of the prefrontal cortex, the orbital and the dorsolateral regions, carry out two distinct but interrelated functions, each having a specific influence on the septal-hippocampal system, in the formation and retrieval of episodic memories.

Orbital prefrontal cortex is primarily connected to the medial thalamus, ventrolateral caudate, the amygdala and the hypothalamus. Importantly for this discussion, it also projects to medial septum and therefore influences hippocampal activity via its potential influence on the cholinergic and GABAergic action of medial septum. The dorsolateral part of the prefrontal cortex is connected to the hippocampus via the cingulate gyrus and more directly via the parahippocampal and entorhinal cortices. Both parts of the prefrontal cortex therefore influence hippocampal activity, but, we suggest, in quite different ways. The dorsolateral part appears to be primarily concerned with the formation and storage of strategies and goals, and our hypothesis is that it influences the learning and recall mechanisms of hippocampus by applying a "top-down priming" action directly through its projections to cingulate gyrus and entorhinal cortex. In this way it influences the selection of which episodes of previously experienced behaviour should be used to create the

prediction of the next sensory event, this selection being determined primarily by previously stored associations between specific episodic memories and the current goal/strategy. Thus the dorsolateral area is primarily concerned with the goal/strategy-directed, flexible association of appropriate episodes of sensory-motor experiences.

We propose that the orbital part is primarily concerned with monitoring the motivational state and the association of reward with sensory input in the behaving animal through its connections with hypothalamus, amygdala and medial thalamus, and influences the hippocampus by providing a high level modulation of the control that medial septum exerts over hippocampal learning and recall.

In the remainder of this paper, we develop the necessary basis for a computational model of predictive information processing in the septal-hippocampal region. In particular, we propose an associative learning process in the synapses that the dentate gyrus granule cell projections make with CA3 principal cells in the rat hippocampus, which is used to demonstrate and support the hypothesis that there exists predictive learning in the hippocampus. We cite experimental evidence for the presence of such predictive learning in the hippocampus, and experimental evidence for temporally asymmetric modification of synaptic efficacy, which provides the basis for the predictive learning mechanism. Finally we describe the major components of the preliminary computational model of this predictive learning process and report on some simulation results from the model.

A Theory of Predictive Learning in the Hippocampus

In a recently proposed theory of spatio-temporal learning in behavioural tasks (Denham and McCabe, 1996; Borisyuk et al, 1999), it was hypothesised that a major function of the hippocampus was to use contextual information about immediate past sensory-action states to form predictions of the upcoming sensory state to be expected from an action currently being taken. It was hypothesised that this predictive capability would enable a comparison to be made between the predicted state and the actual state when it came about, so that novel or unexpected states, i.e. one's which were not part of an animal's anticipated, or "normal", experience in the current context, could be detected. This would enable a mismatch between the predicted and the actual next state to be detected by the hippocampus, which might result in a number of different responses in other regions of the animal's brain, as a result of efferent connections from the hippocampus. For example, a behaviourally inhibitory control might be applied to the motor actions of the animal, through outputs, via the subiculum, to the nucleus accumbens in the basal ganglia. It was also hypothesised that the mismatch event would, via local cholinergic and GABAergic feedback through the medial septum, dynamically control the switch between learning and recall in the hippocampus, as suggested by Hasselmo et al (1995). The GABAergic feedback mechanism via medial septum could also function to control the gating and timing of learning in the hippocampus, modulated by cortical and brain stem septal afferents (Denham and Borisyuk, 1999).

Underpinning this hypothesis, and an important part of the theory described in (Denham and McCabe, 1996), is the postulated learning of a predictive association between the presynaptic activity on the mossy fibre projections of the dentate gyrus (DG) granule cells, and the post-synaptic activity of the CA3 principal cells with which they form synapses. Both DG granule cells and CA3 principal cells receive strong projections from the entorhinal cortex (EC). The EC itself receives its major inputs from the multimodal frontal, parietal and temporal association areas of neocortex, and its activity is held by many to represent the current sensory state of the animal, in some compressed form. Denham and McCabe (1996) proposed that the activity on the mossy fibre projections was a function of both the current sensory state and a short-term history, or context, for that state, and that this presynaptic activity became associated with a slightly later, EC-induced, postsynaptic activity in CA3 cell. After learning, the activity of the DG granule cells would become capable alone of inducing the postsynaptic activity in the CA3 cells, and would do so some time earlier than the time at which it had occurred originally, i.e. at the start of the learning process. Thus the activity of the principal cells in CA3 would come to predict the upcoming position of the animal, as defined by its sensory state at that location.

Experimental Support for the Theory

Experimental support for the predictive nature of the selective "place" firing of CA3 and CA1 principal cells comes from observations by Muller and Kubie (1989). They found that by fitting the spatial firing pattern of CA3 and CA1 pyramidal cells to positions later or earlier than that which the rat was in when they fired, the best fit to the data occurred if it was assumed that the firing must precede the animal's position in time by about 60-100ms.

Further evidence for the predictive capability of CA1/CA3 principal cells was recently obtained by Mehta et al (1997). In their experiment, a large number of such cells were recorded simultaneously from two rats as they ran repeatedly around an elevated closed rectangular track. They observed that the place fields of the recorded cells expanded and shifted in a direction opposite to the direction of movement of the rat on a closed linear track, over a period when the rat travelled the same route on the track several times. They proposed that this result provides evidence of systematic changes in the neuronal firing properties of the cells, and in particular for Hebbian

synaptic enhancement both due to and during the rat's behaviour. They concluded that the backward shift of the place field means that the firing of the cell represents a *prediction* of the rat's anticipated upcoming arrival at the place originally coded for by the cell. Further confirmation of these results has recently been obtained by Zhang et al (1998), in an experiment to reconstruct the position of a rat based on hippocampal place cell activity.

We should note however other explanations for this observed phenomenon has been put forward, in particular by Blum and Abbott (1996) who postulate a mechanism based on potentiation of synaptic connections between place cells with overlapping fields, and a role for the place field shifts in the creation of a navigational map in hippocampus.

Experimental Basis for the Proposed Model of the Predictive Learning Mechanism

Our proposed model of predictive learning derives from some recently reported experimental results (Levy and Steward, 1983; Debanne et al, 1995; Magee and Johnston, 1997; Markram et al, 1997; Debanne et al, 1998; Guo-quiang Bi and Mu-ming Poo, 1998) which have measured the potentiation of both neocortical and CA1 hippocampal pyramidal cells during temporal pairing of EPSPs and backpropagating action potentials (APs). In particular, recent experiments (Magee and Johnston, 1997) have shown that long-term potentiation (LTP) of the synapses of a CA1 pyramidal cell is associative, and is mediated by the pairing of back-propagating APs and sub-threshold EPSPs in the cell's dendritic tree. Other recent experiments (Markram and Tsodyks, 1996; Markram et al, 1997) have shown similar effects in layer 5 pyramidal neurons in neocortex, and, most importantly, have demonstrated that the effect was temporally asymmetric, i.e. *potentiation* of the synapse occurs experimentally if firing of the postsynaptic neuron occurs within a short period of between 10ms and 100ms *after* the spiking of the presynaptic neuron, whereas synaptic *depression* occurs if the postsynaptic cell fires up to 10ms cell *before* the presynaptic neuron.

Whilst we recognise that these experiments were not carried out on the mossy fibre synapses which dentate granule cell make with CA3 pyramidal cells, other recent experimental results lead us to make the assumption that similar mechanisms of associative learning will be evident in CA3 pyramidal cells and their mossy fibre synapses. Indeed, recent experiments have demonstrated that both Hebbian (associative) and non-Hebbian forms of long-term potentiation (LTP) can be induced on the mossy fibre synapses (Jaffe and Johnston, 1990; Urban and Barrionuevo, 1996) whilst previously only induction of non-Hebbian LTP was thought possible (Zalutsky and Nicoll, 1990). In particular, there is evidence of non-NMDA dependent associative potentiation of the mossy fibre synapses of CA3 pyramidal cells, as a result of brief high frequency stimulation (B-HFS = 6-10 pulses at 100Hz repeated 8 times at 5 sec intervals) of the mossy fibre synapse, which is dependent on postsynaptic depolarization (Urban and Barrionuevo, 1996).

We propose that the requirement for temporal asymmetry in the pre- and postsynaptic activity of a CA3 cell would ensure that, after potentiation, the pattern of activation on the mossy fibres of DG will have become associated with the pattern of activation of the CA3 cell, which is induced by the EC input to the cell up to 100ms *after* the activity in DG. We propose therefore that, as learning takes place during repeated exposure to the particular place in the environment, the strengthened EPSP activity due to the mossy fibre projections from DG will eventually induce a pattern of firing of CA3 cells which will predict, a direct result of this temporally asymmetric learning process, the location of the animal up to 100 ms into the future.

To understand how this process might occur, it is necessary to look more closely at the specific changes in EPSP activity which might be taking place in CA3 cells as a result of the potentiation process. Firstly, it is important to note that the projections to a CA3 pyramidal cell from a DG granule cell, via the mossy fibres, form synapses on the proximal part of the apical dendritic tree of the cell, whilst projections from the EC, via the perforant path, form synapses on the distal part of the apical dendritic tree. The need for temporal asymmetry in the potentiation of mossy fibre synapses implies that the projections from the DG must create a subthreshold EPSP which precedes by between 10 and 100ms the APs resulting from the depolarization of the cell by the EC input. Thus the distal EC projections must be more capable initially of generating APs in the cell than the more proximal DG projections. In this respect, we note that in studies of the firing of both cortical and hippocampal pyramidal cells (Miller et al, 1985; Shepherd et al, 1985) it has been observed that synaptic potentials spreading from the distal branches of the dendritic tree appear to be subject to regeneration in local "hot spots" of high Na conductance, the so-called "active dendritic trigger zones". This has the apparent effect of making the distal inputs much more effective in the creation of action potentials at the at the cell body, than proximal inputs, whose responses spread passively. The strength of the direct EC projections and their capability of generating APs in CA3 cells have also bee reported on by Urban et al (1998) and Berzhanskaya et al (1998).

We propose that the pairing of the input from EC, which results in the creation of action potentials in the CA3 cell, with the subthreshold EPSPs produced by the presynaptic activity on the proximal mossy fibre inputs, causes a potentiation of the related synapses. This in turn results in an enhancement of these EPSPs, to the point where they

themselves generate the APs at the axon hillock of the CA3 cell. Thus, over the period of the learning time, the firing of the cell will gradually move forward in time, to occur some time before the time at which the cell originally fired in response to its input from EC, i.e. in response to the rat being in a particular location.

Although we do not include the effect in our current CA3 cell model, we are aware that there is evidence that the septohippocampal GABAergic and cholinergic inputs to the CA3 cells are implicated in the generation of the "theta rhythm", the 8-12 Hz rhythmic EEG signal which can be reliably recorded from rats during locomotion, etc. Further, there is also evidence that increased cholinergic innervation of CA3 cells increases their excitability (e.g. Cole and Nicoll, 1984). It would therefore appear that increased CA1/CA3 cell activity will then lower this cholinergic innervation due to feedback through the medial septum, thus implementing a "gating signal" on the depolarising effect of the perforant path input, every 80-125 ms, i.e. at the theta rhythm. Similar gating effects are generated by the GABAergic inputs from medial septum, which terminate on the inhibitory cells in CA3 and CA1 and have a disinhibitory effect on the pyramidal cells in these regions, as described in (Denham and Borisyuk, 1999). Both these mechanisms would therefore provide the basis for a natural gating of the sensory state input to the CA3 principal cells from EC via the perforant pathway, and a natural time period over which the prediction of the up-coming sensory state can be learnt. This is consistent with the experimental results on extent of the predictive firing of CA1/CA3 principal cells (60-120 ms) cited above.

A Computational Model of Predictive Learning in Pyramidal Cells

To demonstrate the principle of predictive learning, we have built a computational model of the process, initially for a single principal cell, based upon a leaky integrate-and-fire neuron model, in conjunction with a dynamic synapse model and a recently developed learning rule for up and down regulation of dynamic synapses (Denham and McCabe, 1998). This composite model closely replicates the experimental results on temporally asymmetric potentiation of pyramidal cells through the pairing of subthreshold EPSPs and backpropagating APs obtained recently by Markram and his colleagues (Markram and Tsodyks, 1996; Markram et al, 1997). These results demonstrated that changes in the amplitude of a presynaptically generated, subthreshold excitatory postsynaptic potential (EPSP) can be differentially up- or down-regulated, depending on the precise timing of the postsynaptic back-propagating action potential (AP) relative to the EPSP, at a single modifiable synapse.

In particular, Markram et al (1997) demonstrated that in order for synaptic efficacy to be enhanced it is necessary for the postsynaptic AP to follow the presynaptically-generated EPSP by between about 10 and 100 ms. If the postsynaptic AP instead precedes the EPSP, then the efficacy of the synapse may be decreased. They also show that the increase in synaptic efficacy is also dependent on the frequency of the AP-EPSP pairs, with a sharp increase in efficacy at 10 Hz. The learning rule described in (Denham and McCabe, 1998) differentially modifies the synaptic efficacy parameter in the dynamic synapse model, as a function of the instantaneous amplitude of the back-propagating postsynaptic (AP), gated by the thresholded amplitude of the EPSP. We have shown (Denham and McCabe, 1998) that this learning rule results in the required form of both up- and down-regulation of the synaptic efficacy, and displays both the temporal and frequency dependence evident in the experimental results of Markram et al (1997). A detailed description of the model can be found in (Denham and McCabe, 1998; Borisyuk et al, 1999) and is beyond the scope of this paper. However we describe below its main features.

The model uses a leaky integrate-and-fire neuron model to produce an idealised form of back-propagating AP, which the learning rule pairs with the EPSP at a single active synapse in order to produce the modification of the efficacy of the synapse. The EPSP is generated by a dynamic synapse model, originally proposed by Grossberg (1968, 1969), and recently described by Tsodyks and Markram (1997), where it was used to model the activity-dependent redistribution of synaptic efficacy experimentally observed in the pairing experiments of Markram and Tsodyks (1996) and Tsodyks and Markram (1997). The learning rule was introduced in (Denham and McCabe, 1998) and is based upon the continuous temporal relationship between the back-propagating AP and the EPSP, and is used to up- or down-regulate an efficacy parameter in the dynamic synapse model.

To model the effect of a backpropagating AP on an active synapse, we combine the dynamic synapse model which generates the EPSP, with the neuron model which generates the AP in the postsynaptic cell. It is important to the learning rule that this AP displays both the depolarizing and hyperpolarizing portions of the signal, which are present in the biological AP. The hyperpolarising portion is not always included in neuron models which explicitly generate action potentials, i.e. the class of so-called "integrate-and-fire" neuron models. We use a simple, single compartment neuron model, which ignores the specific mechanisms and structure of the dendrites of the cell, although these have been shown by Magee and Johnston (1997) to play a role in modifying the amplitude of the back-propagating AP, and will need to be included in any future, more biologically realistic model..

The learning rule (Denham and McCabe, 1998) uses the instantaneous amplitude of the back-propagating AP, gated by the thresholded presence of the presynaptically generated EPSP, to up- and down-regulate the value of the synaptic efficacy in the dynamic synapse model, thus

making the change in efficacy at any time dependent on the precise temporal relationship between the backpropagating AP and the EPSP, and value of synaptic efficacy at any time dependent on both the present and past activity of the neuron and its presynaptic input.

Using this learning rule, it is shown in Denham and McCabe (1999) that the computational model described above produces similar frequency dependence characteristics (Figure 1: lower graph) to the experimental data in Markram et al (1997), (Figure 1: upper graph), i.e. the amount of potentiation of the synapse increases with increasing frequency of the EPSP-AP pairs. The model is also able to replicate closely (Figure 2: lower graph) the experimental results of Markram et al (1997) (Figure 2: upper graph) which showed that different relative timing of the EPSP and the back-propagating AP can cause either an increase or a decrease in synaptic efficacy. In both these graphs, a relative timing of either +100ms or -100ms results in no change in synaptic efficacy, whereas relative timings of +10ms and -10ms show an increase and a decrease in synpatic efficacy, respectively.

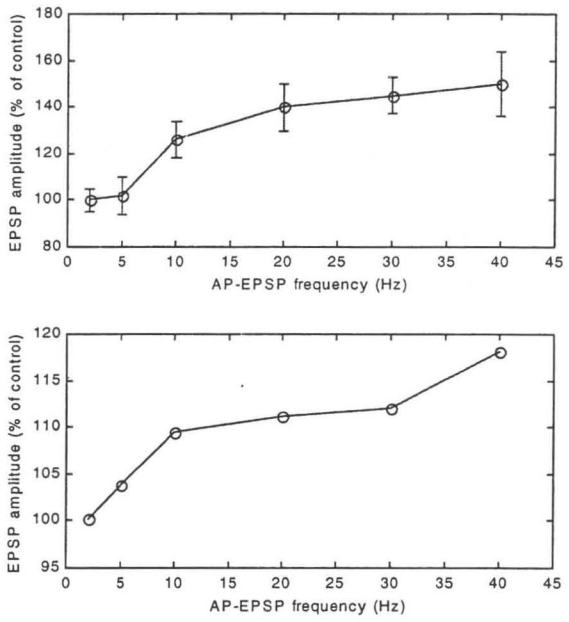

Figure 1. Frequency dependence of the synaptic potentiation shown experimentally by Markram et al (1997) (upper graph) and by the model described in Denham and McCabe, 1998 (lower graph)

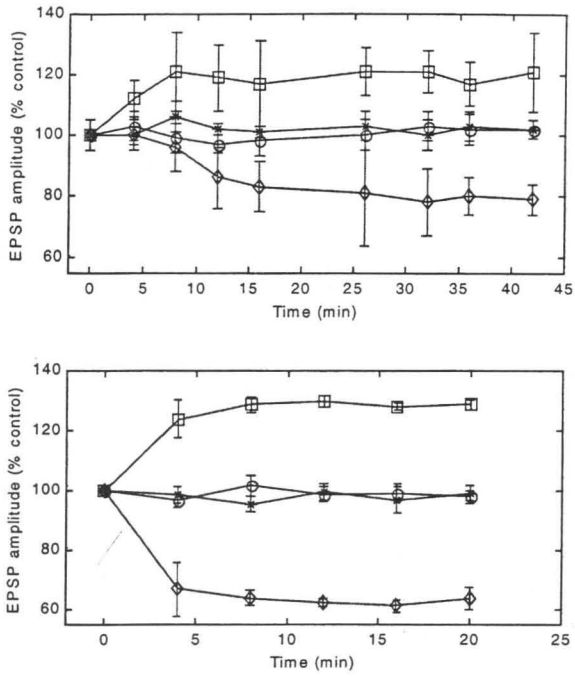

Figure 2. Temporal dependence of regulation of synaptic efficacy as shown experimentally by Markram et al (1997) (upper graph) and by the model described in Denham and McCabe, 1998 (lower graph)

Conclusions

In this paper we have presented a hypothesis for the primary role of the septal-hippocampal region, in information processing in the brain. We have identified this region as being crucial for the ability of an animal to detect instability in its environment, either as a result of changes in the sensory cues it receives in a familiar environment, or on entering an unfamiliar environment. This role of the septal-hippocampal region is essential for the proper control of activity in other brain regions, in particular in the proper establishment of long-term memories, and in the control of the behaviour of the animal when faced with novel situations. We hypothesise that without a properly functioning of the septal-hippocampal region the animal is incapable of distinguishing novel from familiar sensory cues in the context of ongoing behavioural activity. This will result in serious deficiencies in, for example, spatial navigation tasks, as has been observed in a large number of experiments over many years (e.g. O'Keefe and Nadel, 1978).

We suggest that learning and memory processes are the fundamental basis of all information processing in neural systems, and that in order to build computational architectures which are capable of behaving like biological

neural systems, we must understand the mechanisms in the brain that make our learning and memory processes operate in such a fast and efficient manner. The goal of our work, from the viewpoint of neural computation, is thus to devise computational architectures which display the kind of selective fast learning and recall of memories which are evident in the brain and which are the fundamental basis for perception and action.

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