A simulation of parahippocampal and hippocampal structures guiding spatial navigation of a virtual rat in a virtual environment: A functional framework for theta theory.

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INTRODUCTION

Behavioral data indicates a role for parahippocampal regions in memory guided behavior in both spatial navigation tasks (Hagan et al., 1992) and matching tasks (Otto and Eichenbaum, 1992; Tang et al., 1997). Physiological data shows the patterns of activity in parahippocampal regions during performance of these tasks (Young et al., 1997; Suzuki et al., 1997; Frank et al., 2000) and also illustrates the cellular physiological properties which could be important for memory function (Klink and Alonso, 1997; Fransen et al., 2001).

Computational modeling provides a useful means of linking behavioral data to the physiological data. Most previous models of the hippocampal formation do not explicitly represent an animal interacting with its environment, focusing instead on static abstract representations of sensory input and motor output (McNaughton and Morris, 1987; Treves and Rolls, 1994; Levy , 1996; Wallenstein and Hasselmo, 1997; Wu et al., 1998). These models make many assumptions about the timing of input and output. These assumptions can be reduced if the network directly interacts with an agent moving through an environment. Here we present modeling work in which a neural simulation which includes parahippocampal regions guides the movements of a virtual rat in a virtual environment. This type of modeling provides a useful technique, elucidating specific problems for guiding behavior, and allowing determination of biological realistic solutions to those problems.

BEHAVIORAL TASK

This simulation was developed within a general purpose neural simulation package developed by Robert Cannon under the name "catacomb" (DeSchutter, 2000; Cannon, 2001). This package allows flexible creation of multiple different environments including arbitrary barrier locations, and arbitrary locations for individual objects. A virtual rat can be placed into a given virtual environment, and its movements can be controlled in one of three ways: 1.) according to pre-determined trajectories, 2.) with random choice of direction and speed of movement, and 3.) with output from a neural simulation. Numerous parameters of the environment and rat can be adjusted within the simulation.

In this chapter, we will present an example of modeling the behavior of a rat in a T-maze reversal task (M'Harzi et al., 1987). In this task, the rat is placed in the stem of the maze, and food reward is placed in one arm of the maze (e.g. the left arm). On initial training trials, the rat learns to find the food reward in this arm of the maze. After the initial learning trials, there is a reversal of food reward location, so that all subsequent trials involve placement of food reward in the opposite arm of the maze (e.g. the right arm). Initially, the rat makes errors going to the initially learned location, but eventually it starts to explore the maze more and finds the new food reward location. On subsequent trials, it must respond on the basis of this new food location (the right arm), despite the initial well-learned location (the left arm).

FIGURE 1 ABOUT HERE.

INTERFACE BETWEEN NEURAL SIMULATION AND VIRTUAL RAT

The catacomb system describes the environment of this T-maze in terms of solid walls and reward locations. A number of different practical problems needed addressing in guiding the movements of the virtual rat in this virtual T-maze. For example, many simplifying

assumptions were made about the processing of sensory input and the production of motor output. In the simulation, as the rat moved through the maze, information about its location (place) and its proximity to food reward (proxim) were sent from the virtual rat to the neural simulation, as shown in Figure 2. This information was sent directly, though it would be mediated by a number of stages of sensory processing. The place signal represents information encoded by "place cells", which are a well-described physiological property of hippocampal and parahippocampal units. During recording of individual action potentials ("units") from these regions, individual neurons are found to respond on the basis of the location of the rat within the environment (O'Keefe and Dostrovsky, 1971; McNaughton et al., 1983; Muller et al., 1987; Eichenbaum et al., 1989; Barnes et al., 1990; Quirk et al., 1992; Wood et al., 2000; Frank et al., 2000). In the simulation presented here, the environment is discretized into square approximations of place fields. A walled T-maze is defined with a stem that is three place fields in length, and with two arms which are two place fields in length. A food-reward is placed at the end of the left arm of the T-maze.

FIGURE 2 ABOUT HERE.

It is possible to model the formation of place cell responses through self-organization of sensory input to the network (Sharp, 1991; Kali and Dayan, 2000), and ultimately these features can be incorporated in our model. But at this point, we are not modeling the formation of place cell responses, instead assuming that this information is available to the circuit. However, the structure of the model was constrained by the available data on the region of the environment in which place cells would fire, known as the "place field" of a cell. Experimental data indicates that the place fields for cells in hippocampal region CA1 are much smaller than the place fields for cells in the entorhinal cortex (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000).

The output of the simulation guided the movements of the virtual rat in the virtual environment, as summarized in Figure 2. This output took the form of neural firing representing the next desired location of the rat. In the simulation, this next desired location was obtained from hippocampal region CA1, and the virtual rat moved directly toward the next desired location. This obviously greatly simplifies the many stages of motor output in the brain. In particular, as an initial step in processing this next desired location should probably interact with information about head direction and current location to be transformed into a signal for turning and speed of movement. Other models have made this translation from place representation to turning direction (Sharp et al., 1996; Burgess and O'Keefe, 1996; Burgess et al., 1997; Redish and Touretzky, 1998), and these stages could be incorporated into future versions of the model presented here.

FUNCTIONAL PROBLEMS AND PHYSIOLOGICAL SOLUTIONS

As noted above, the simulations were very useful for defining specific functional problems and providing a structure in which solutions to these problems could be determined while meeting the constraints of physiological data. In this section, we will focus on three specific major problems concerning the dynamics of the neural simulation. The three problems are as follows:

Problem #1: Sensory input comes in at a slower pace than the window of synaptic modification.
Solution: Buffering activity in entorhinal cortex allows effective encoding.
Problem #2: Encoding can suffer from interference due to retrieval.
Solution: Separation of encoding and retrieval on different phases of theta rhythm.
Problem #3: Movement toward goal requires interaction of goal and current location.
Solution: Convergent input from entorhinal cortex and region CA3 allows selection of next desired destination.

Discussion of these problems illustrates stages in the construction of the model.

1. BUFFERING OF SENSORY INPUT

To reduce computing time, the initial encoding of the environment occurs with the virtual rat traversing a pre-coded trajectory through the T-maze. This brings the rat up the stem of the maze, into the left arm, back to the stem, up into the right arm and back to the original starting position in the stem. This represents the stage of initial exploration necessary to obtain effective behavior by any rat in a spatial environment.

The first problem arises because there is a fundamental discrepancy between the rate of behavioral transitions between sensory events in the environment and the temporal requirements of long-term potentiation. Data indicates that long-term potentiation is obtained with relatively brief delays between the pre-synaptic spike and the post-synaptic spike. Optimal delays for induction of long-term potentiation are usually less than 40 msec (Levy and Steward, 1983; Bi and Poo, 1998; Markram et al., 1997), with no LTP occurring at delays of 100 msec (Markram et al, 1997; Bi and Poo, 1998). In the neural simulations presented here, these time courses have been utilized explicitly as a synaptic modification function, with a duration of about 35 msec. In contrast, transitions between different locations in the environment or between different stages of a behavioral task will take several hundred milliseconds. In order for LTP to occur, the information about preceding behavioral events must be held in a buffer so that it can occur within the 35 msec delay with the most recent sensory input. In addition to the problem of slow behavioral transitions between locations, there is the problem of situations where a rat stops temporarily in the maze, and as discussed below if there are separate phases of encoding and retrieval within theta cycles, the buffer must bridge across periods of retrieval.

The neural simulation presented here uses intrinsic mechanisms in entorhinal cortical neurons to maintain a buffer of sensory input from the environment, as shown in Figures 3 and 4. This solution has support from extensive physiological data obtained from brain slice preparations of the entorhinal cortex, which show that activation of muscarinic receptors induces calcium sensitive cation currents which can provide a mechanism for sustained repetitive action potential firing in single neurons (Alonso and Klink, 1993; Klink and Alonso, 1997a, 1997b). These currents have been tested in detailed biophysical simulations of entorhinal cortical neurons and shown to provide the necessary intrinsic mechanisms for self-sustained activity of individual neurons (Hasselmo et al., 2000; Fransen et al., 2002). In more abstract simulations, the afterdepolarization caused by these currents can mediate working memory for sequences (Jensen and Lisman, 1996b). These intrinsic currents provide a potential

mechanism for phenomena observed in single unit recording from the entorhinal cortex during performance of delayed matching and delayed non-matching tasks (Suzuki et al., 1997; Young et al., 1997). In particular, if cholinergic modulation is present, these cation currents are activated. Figure 3 shows the self-sustained spiking activity of a modeled neuron. The spiking of a neuron in response to sensory input causes calcium influx which further activates the current, causing depolarization which persists even after the sensory input has terminated (Fransen et al., 2002). Each new spike causes further calcium influx and further activation of the current, allowing persistent activity for extended periods after the initial depolarization caused by sensory input. Eventually the sustained spiking activity can be terminated by calcium induced desensitization of the current, or by calcium activation of other currents such as the calcium-activated potassium current.

FIGURE 3 ABOUT HERE

As the virtual rat moves through the environment, place cell representations in entorhinal cortex layer II are sequentially activated. The intrinsic cation currents are represented with a sequence of dual exponential potential changes following each action potential. There is an initial fast afterhyperpolarization, preventing immediate spiking. There is a slower afterdepolarization which causes the cell to come back up to firing threshold and emit another spike. This could continue to generate spikes, but the persistent spiking must be terminated or it will cause excessive buildup of spiking activity. Therefore a third dual exponential potential with an even slower time course is added to the simulation. This terminates the firing of the neurons after they each generate three spikes. This sequence of self-sustained firing allows the network to hold a spiking representation of the preceding location for a sufficient time to allow spikes representing previous location and spikes representing current location to fire at less than a 35 msec delay, as shown in Figure 4. This activity from entorhinal cortex layer II spreads to entorhinal cortex layer III and to region CA3 of the hippocampus, where the short firing interval allows Hebbian synaptic modification of excitatory recurrent connections. The strengthening of these excitatory recurrent connections encodes the environment in the form of associations between adjacent spatial locations, as shown in Figure 5. Note that we have not yet incorporated simulations of the dentate gyrus into this model. In addition, we assume that dendrites extent of layer III neurons allows sufficient connectivity with layer II recurrent connections or afferent input to allow the encoding of pathways within layer III circuits.

FIGURE 4 ABOUT HERE.

2. SEPARATION OF ENCODING AND RETRIEVAL

In addition to the requirement for buffering information, encoding of the environment requires other features to prevent interference from prior retrieval. As noted above, the initial encoding of the environment occurs with the virtual rat traversing a pre-coded trajectory through the T-maze. As the rat moves along this trajectory, it causes sequential spiking of adjacent place cell representations in layer II of entorhinal cortex, and this activity causes sequential spiking in separate populations representing entorhinal cortex layer III and region CA3 of the hippocampus. These regions do not contain the intrinsic mechanisms for self-sustained activity in the simulation, but are driven by the input from neurons with these

mechanisms. Region CA3 and EC layer III contain initially weak all-to-all excitatory connections which are strengthened whenever a presynaptic spike occurs less than 35 msec before a postsynaptic spike. This allows formation of a representation of the environment in both layer III and region CA3 in the form of strengthened connections between place cells representing adjacent locations, as shown in Figure 5. The encoding of associations between adjacent locations corresponds to the encoding of sequences which was previously modeled as a function of recurrent connections in region CA3 (Marr, 1971; McNaughton and Morris, 1987; Levy, 1996; Wallenstein and Hasselmo, 1997).

FIGURE 5 ABOUT HERE

This encoding process runs into serious difficulties unless the spread of activity across excitatory recurrent connections is suppressed during encoding. This problem is illustrated on the right side of Figure 5. If spiking can spread across previously modified synapses, then retrieval starts to occur as the rat is still encoding the environment. For example, after entering the left arm of the maze, the rat returns to the stem of the maze. As the rat moves up the stem of the maze, the spiking activity in the stem of the maze spreads across previously modified synapses to cause spiking of place cells representing the left arm of the maze. This causes strengthening of multiple additional undesired associations between place cells representing the stem of the maze and place cells representing non-adjacent locations in the left arm of the maze.

Theta rhythm may separate encoding and retrieval.

The interference shown in Figure 5 is caused by retrieval during encoding. This interference can be prevented by suppression of retrieval during encoding, which is how the effective encoding on the left side of Figure 5 was obtained. The suppression of retrieval during encoding requires separate dynamics in the network during encoding and retrieval. We propose that the separation of encoding and retrieval dynamics may occur physiologically at different phases within each cycle of the hippocampal theta rhythm. The hippocampal theta rhythm is a 3-12 Hertz oscillation observed in the EEG of the hippocampus during specific behavioral phases. In rats, theta rhythm primarily appears when the animal is actively exploring the environment (Buzsaki et al., 1983). The theta rhythm is reduced in amplitude when the rat is motionless, or performing consummatory behaviors such as eating or grooming. In rabbits and cats, theta rhythm can appear when the animal is sitting motionless, but specifically when the animal is attending to behaviorally relevant stimuli (Berry and Thompson, 1978).

The theta rhythm results from physiological changes which could be ideal for switching between encoding and retrieval dynamics. The theta rhythm oscillations in the EEG reflect changes in the distribution of synaptic currents within the hippocampus (Stewart and Fox, 1990; Brankack et al., 1993; Bragin et al., 1995). As summarized in Figure 6, these changes are consistent with a separate phase of encoding (with strong afferent input from entorhinal cortex to region CA3 and CA1), and a phase for retrieval (with strong synaptic transmission at recurrent connections in region CA3 and from region CA3 to region CA1).

As shown on the left side of Figure 6, one phase of theta could provide appropriate dynamics for encoding. Effective encoding would require strong excitatory input conveying information about sensory input from entorhinal cortex. In experimental work, current source density analysis (Brankack et al., 1993; Bragin et al., 1995) shows strong current sinks in stratum lacunosum-moleculare (s. l-m) of region CA1 at the time of the trough of the EEG recorded at the fissue (right near the border of s. l-m and the dentate gyrus). These strong current sinks could result from the greater spiking activity in entorhinal cortex layer III at this time, consistent with unit recordings from entorhinal cortex in awake animals (Stewart et al., 1992; Quirk et al., 1992; Frank et al., 2002) and in anesthetized animals (Alonso and Garcia-Austt, 1987). They could also be due to changes in the magnitude of synaptic transmission due to modulation of synaptic transmission. For example, activation of presynaptic metabotropic glutamate receptors has been shown to more strongly suppress synaptic transmission in s. l-m than in s. radiatum (Hasselmo and Cekic, unpublished data), this could cause phasic changes in levels of glutamatergic release in s. l-m. These strong current sinks would provide a strong influence of sensory input at a time when synaptic modification is strong, as discussed below.

As shown on the right side of Figure 6, a separate phase of theta could allow retrieval dynamics. In contrast to the encoding input from entorhinal cortex, some of the current sinks observed in stratum radiatum (s. rad.) appear about 180 degrees out of phase with the s. l-m sink (Brankack et al., 1993). This is consistent with the fact that pyramidal cells in region CA3 and region CA1 fire maximally at the peak of the fissure EEG (Fox et al., 1986; Skaggs et al., 1996), when entorhinal input is weaker. This suggests that region CA3 provides a strong driving force for spiking of CA1 pyramidal cells at the phase when entorhinal input is relatively weak, whereas this input from region CA3 is weaker when the entorhinal input is strong. The changes in magnitude of current sinks in stratum radiatum could be due to changes in amount of presynaptic spiking, but they could also be due to changes in the magnitude of synaptic transmission. This is consistent with the evidence for a systematic change across the theta cycle in the magnitude of evoked population spikes (Rudell et al., 1980; Buzsaki et al., 1981; Rudell and Fox, 1984) and in the magnitude of evoked excitatory postsynaptic potentials (Wyble et al., 2000). Those experiments suggest that even with a consistent stimulation amplitude, the amount of synaptic transmission present in stratum radiatum is reduced at the peak of the local EEG, which is the trough of the fissure EEG, and the time of strongest synaptic transmission from entorhinal cortex. In summary, the spread of activity in region CA3 mediating retrieval could be strongest at the phase when entorhinal input is weakest.

FIGURE 6 ABOUT HERE.

In order to prevent retrieval from interfering with encoding, the synaptic transmission associated with retrieval should be weakest at the time that these synapses are undergoing synaptic modification (LTP). This requirement may seem somewhat paradoxical, as it is normally assumed that stronger synaptic transmission will cause stronger synaptic modification. However, the available physiological data supports this requirement. A number of experiments have tested the induction of long-term potentiation at different phases

of the theta rhythm recorded from the electrode being used to record evoked potentials as well (Pavlides et al., 1988; Holscher et al., 1997; Orr et al., 2001; Wyble et al., 2001). These experiments all show the best induction of long-term potentiation at the peak of the local EEG, which should correspond to the time of weakest local synaptic transmission. In particular, induction of LTP in stratum radiatum of region CA1 is strongest at the time when synaptic transmission at these synapses is the weakest (Holscher et al., 1997; Wyble et al., 2001; Hasselmo et al., 2002a). Similar effects appear during induction of theta rhythm oscillations in slice preparation (Huerta and Lisman, 1993). The simulation presented here provides a clear functional framework for this data on the relative phase of these physiological variables. Encoding of the environment will be most effective if synaptic modification of connections arising from region CA3 is strongest at the time that synaptic transmission at these synapses is weakest. In contrast, experiments show that stimulation at the trough of the theta rhythm causes depotentiation or long-term depression (Holscher et al., 1997; Wyble et al., 2001). This could allow retrieval to cause forgetting if the retrieved activity does not match with current sensory input.

These changes are also consistent with changes in pyramidal cell membrane potential during theta rhythm in region CA1 (Fox, 1989; Kamondi et al., 1998). The potentiation of synapses in stratum radiatum will be enhanced when entorhinal input causes depolarization of apical dendrites, but physiological data shows that pyramidal cell somas are hyperpolarized when dendrites are depolarized (Kamondi et al., 1998). In contrast, during a retrieval phase, the soma membrane potential will be depolarized allowing spiking output from retrieval at a time when dendritic depolarization is decreased.

This hypothesis about the function of relative phases of physiological variables is supported by behavioral data. Extensive data suggests that the theta rhythm is paced by neuromodulatory input from the medial septum (Stewart and Fox, 1990; Toth et al., 1997). This neuromodulatory input arrives via fibers of the fornix, so that lesions of the fornix greatly reduce the amplitude of hippocampal theta rhythm (Buzsaki et al., 1983). In the simulation presented here, loss of theta rhythm would be expected to result in impairment of new encoding due to interference from retrieval of previous associations. Thus, there might be an enhancement of proactive interference. If a rat learns a particular spatial response in a behavioral task, it might be more difficult for the rat to change that spatial response after reversal. In behavioral studies, lesions of the fornix have been demonstrated to impair performance in spatial reversal tasks. Lesions of the fornix allow learning of the initial location, but fornix lesioned rats show a greater number of errors when the location of the food reward is moved to the opposite arm of the maze (M'Harzi et al., 1987).

The role of theta rhythm in spatial reversal learning has been analyzed in a simplified mathematical representation of the hippocampal circuits encoding associations in the T-maze (Hasselmo et al., 2002a). In this analysis, associations between location and food are encoded when food is encountered in one arm of the maze. Oscillatory functions with variable phases are used to represent changes in afferent synaptic transmission at synapses from EC layer III to region CA1 and at synapses between region CA3 and CA1 storing associations, as well as the change in strength of synaptic modification at the synapses from region CA3 to CA1. The performance of the network is evaluated with regard to how much the response after reversal

resembles the correct reversal association versus the initial learned association. As shown in Figure 7, the best performance occurs when the oscillations of synaptic modification (LTP) are in phase (0 degrees) with the oscillations in afferent input from EC, but are out of phase (180 degrees) with oscillations at the modifiable synapses from CA3.

FIGURE 7 ABOUT HERE.

General property of theta rhythm timing in multiple different regions.

The explicit timing of synaptic transmission at different pathways in region CA3 and region CA1 greatly enhances the function of the model. This same principle of phasic changes in physiological properties may extend to other parameters within these regions, and to physiological parameters in a number of other regions. The functional properties of the simulation provide a framework for understanding the phase relationships of physiological parameters in different regions. In a sense, it provides a functional framework for a comprehensive theta theory, which can describe optimal phase relationships between multiple different regions.

Already, the simulation requires specific phase relationships of a number of different parameters in different regions, in order to transmit the activity necessary for separate dynamics of encoding and retrieval. In particular, to accurately encode the environment, the flow of sensory information from the environment to the hippocampus must be maximal during the phase when synaptic modification (LTP) is maximal at recurrent synapses encoding the environment. Thus, in the simulation, the following parameters have theta modulation with a maximum near the phase of encoding (which corresponds to the trough of theta recorded in the EEG at the hippocampal fissure).

Maximum at encoding:

1. LTP at recurrent synapses in region CA3
2. LTP at recurrent synapses in EC layer III
3. Synaptic transmission from EC layer III to region CA1
4. Synaptic transmission from place cell representation to EC layer II
5. Membrane depolarization in EC layer II (to ensure that buffer sends spikes to CA3 and EC layer III at the appropriate time for encoding).
6. Membrane depolarization of apical dendrites in region CA3 and CA1. (This allows Hebbian long-term potentiation with stratum radiatum inputs, but does not cause spiking in the hyperpolarized cell bodies).

In contrast, to prevent retrieval from interfering with encoding, the retrieval of previously stored information must be maximal during the retrieval phase. This requires that synaptic transmission at excitatory recurrent synapses in region CA3 and EC layer III be maximal during retrieval. In addition, the spiking activity of prefrontal cortex (PFC) needs to be maximal at this phase, as this activity brings information about goal location into EC layer III to provide the goal directed nature of retrieval activity. Recordings in prefrontal cortex show that neurons in this region change their firing dependent upon the reward significance of specific stimuli (Thorpe et al., 1983), and individual neurons in hippocampus show responses during approach to goals (Eichenbaum et al., 1987). Anatomical data demonstrates input

from medial prefrontal cortex to superficial layers of entorhinal cortex (Rempel-Clower and Barbas, 2000).

Maximum at retrieval:

1. Synaptic transmission at recurrent synapses in region CA3
2. Synaptic transmission at recurrent synapses in EC layer III
3. Synaptic transmission from region CA3 to region CA1.
4. Synaptic transmission from prefrontal cortex (PFC) to EC layer III (to induce start of retrieval process).
5. Synaptic transmission from region CA1 to output region guiding movement.
6. Membrane depolarization in PFC (to ensure that goal retrieval activity is sent to EC layer III during retrieval phase).
7. Membrane depolarization of cell bodies in region CA3 and CA1, to allow retrieval spiking in response to stratum radiatum input.

Thus, in addition to the phase relationships required within the hippocampus, the separation of encoding and retrieval proposed above provides a general framework requiring specific phase relationships of physiological variables in a number of different brain regions. The separation of encoding and retrieval dynamics was initially inspired by evidence on theta rhythm from hippocampus, but once the oscillatory dynamics were included in the hippocampal simulation it became clear that additional regions needed to have specific phase relationships relative to hippocampal theta rhythm. Exciting recent work has demonstrated potential mechanisms for the synchronization of other regions with theta rhythmic activity. Research has shown theta rhythmic firing of neurons in the basal forebrain correlated with field potentials in neocortical regions (Manns et al., 2001). In addition, research has shown rhythm activity in prefrontal cortex (Demiralp et al., 1994). Vertes has suggested that theta rhythm activity in medial prefrontal cortex could be synchronized with hippocampal theta by strong projections from the nucleus reuniens of the thalamus. There are strong projections in both directions between the nucleus reuniens and the medial prefrontal cortex (Vertes, 2001; McKenna and Vertes, submitted), and the nucleus reuniens has been shown to send strong and selective projections to the entorhinal cortex and to the distal dendrites of region CA1 pyramidal cells (Wouterlood et al., 1990; Wouterlood, 1991). Thus, this circuit provides a potential mechanism for synchronization of physiological activity in entorhinal cortex, region CA1 and prefrontal cortex. The simulation presented here shows how effective performance in specific behavioral tasks depends upon theta synchronization of multiple regions. Thus, the functional framework presented here provides a functional theta theory which generates testable predictions about phasic activity in other regions.

Neuropsychological evidence suggests that damage to the regions involved in synchronization of theta rhythm activity may cause memory impairments. In particular, Vertes has shown that the theta rhythmic output of the hippocampus causes strong theta rhythmic activity in the mammillary bodies (Kocsis and Vertes, 1994). The mammillary bodies show atrophy caused by thiamine deficiency in a rat model of Korsakoff's amnesia (Mair, 1994), suggesting that damage to these structures may contribute to the severe anterograde amnesia found in Korsakoff's amnesia. Of particular interest, Korsakoff's amnesics show strong proactive interference effects in memory tasks (Cermak and Butters, 1972), which are analogous to the

encoding impairment in the T-maze shown here (in Figure 5). This suggests that damage to structures receiving theta rhythmic output from the hippocampus could cause encoding and retrieval dynamics to become confounded, resulting in increased proactive interference. A survey of thalamic damage causing amnesic symptoms suggests that the critical structure associated with amnesic effects is the mammillothalamic tract (Van der Werf, 2000), further supporting the important mnemonic role of circuits involved in theta rhythmicity.

Relation to effects of acetylcholine.

The separation of encoding and retrieval dynamics can be obtained through a variety of different physiological mechanisms, which could act simultaneously. In previous work from this laboratory, it was proposed that the effects of acetylcholine set appropriate dynamics for encoding, through suppression of glutamatergic transmission at excitatory recurrent synapses (Hasselmo and Bower, 1993; Hasselmo and Schnell, 1994; Hasselmo, 1999). However, recent work in this laboratory shows that the time course of the cholinergic modulation of glutamatergic transmission is relatively slow. A brief pulse of acetylcholine followed 100 msec later with the muscarinic antagonist atropine causes a slow onset of suppression over 3-4 seconds, and a persistent suppression for 10 to 20 seconds (Hasselmo and Fehlau, 2001). This is too long a period to allow rapid transitions between encoding and retrieval. Instead, this suppression by acetylcholine coupled with its role in induction of theta rhythm may cause a period of enhanced dynamics for both encoding and retrieval, whereas low levels of acetylcholine may allow appropriate dynamics for consolidation of previously stored information (Hasselmo, 1999).

3. CONVERGENCE OF GOAL LOCATION AND CURRENT LOCATION

The third problem presented here concerns the central issue of goal directed spatial navigation. Once the virtual rat has learned a representation of the environment and the location of the goal within that environment, it needs to use the goal location to guide its movement. The simulation is able to guide the movement of the virtual rat through the virtual T-maze, as summarized in Figure 8. The virtual rat starts at the bottom of the stem of the maze, moves up the stem of the maze, makes the correct left turn at the choice point, and moves to the end of the arm to the reward location.

This goal directed navigation requires more than just the association between adjacent places. It requires that output of the network somehow be influenced by information about the desired goal location and the current location. Several models have addressed this issue by learning a fixed goal location during learning of the environment, such that associations in the network are biased toward a particular goal location (Blum and Abbott, 1993; Gerstner and Abbott, 1998). However, these models do not allow flexible retrieval of multiple possible goal locations in a single environment. We all encounter this problem on a daily basis. When we leave our office door, we guide our next steps on the basis of multiple possible goals during the day, at 10 a.m. it might be a classroom, at 12 noon it might be a restaurant, at 5 pm it might be our home. How can a network guide the choice of next destination based on a distant desired goal? Here we present a potential mechanism for spatial navigation guided by variable goal locations and variable current locations. The goal-neutral representation of the

environment in these simulations is consistent with stability of place cell responses when goal is moved (Speakman and O'Keefe, 1990).

FIGURE 8 ABOUT HERE.

As illustrated in Figure 8, the network uses convergence of associations spreading from the goal location and associations spreading from the current location. The spread of associations from the goal location in many directions is mediated by entorhinal cortex layer III. The spread from current location outward in many directions is mediated by region CA3. The convergence of these associations in region CA1 of the hippocampus allows selection of the next step in the shortest pathway to the closest goal. Convergence of activity in region CA1 has previously been suggested as an important mechanism for matching of retrieval with current input (Eichenbaum and Buckingham, 1989; Hasselmo and Schnell, 1994; Hasselmo and Wyble, 1997).

Entorhinal cortex layer III:
This region is activated by the goal location in prefrontal cortex. Each time this goal location is activated, the activity spreads from the goal location across the connections of the network, as shown in the row showing EC layer III in Figure 8. The broad spread of activity within this network results in a much larger place field representation for individual cells in the entorhinal portion of the model, consistent with data from recordings of the entorhinal cortex (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000). In the model, the pattern of activity in entorhinal cortex layer III causes subthreshold activation of layer II and region CA1.

Entorhinal cortex layer II:
This region receives subthreshold input from the current location, as well as subthreshold input from entorhinal cortex layer III. When the backward spread from the goal converges with the input of current location, this causes spiking activity corresponding to current location at the appropriate time. This activity then causes suprathreshold activation of region CA3.

Region CA3:
When region CA3 receives suprathreshold input from entorhinal cortex layer II, the spiking activity spreads forward along strengthened excitatory recurrent connections corresponding to previously encoded pathways through the environment, as shown in the row illustrating region CA3 in Figure 8. The spread of activity is terminated by activation of feedback inhibition which prevents excessive spread of excitation within the region (corresponding to the relatively small size of place fields for neurons recorded in region CA3). Synaptic output from region CA3 causes subthreshold activation of region CA1.

Region CA1:
This region receives subthreshold input from both region CA3 and entorhinal cortex layer III. Neurons in this region only spike when they receive simultaneous input from region CA3 and entorhinal cortex layer III, as shown in the row illustrating region CA1 in Figure 8. This input is accurately timed such that it only causes spiking when the forward spread from current

location matches the backward spread from goal which activated the current location. Excessive spiking activity is prevented by feedforward inhibition of region CA1 neurons by the output of region CA3. This activity in region CA1 causes spiking corresponding to the next location a rat needs to enter in order to start moving toward its goal. For each new current location, the cycle repeats to allow updating of the next desired location.

Theta phase precession.

An advantage of the simulation presented here is that it can be directly related to available experimental data. Because the simulation uses a network of spiking neurons to guide spatial behavior, the activity in the simulation can be analyzed in exactly the same manner as the recording of place cells from the hippocampus in awake behaving rats. This allows the pattern of activity in the simulation to be directly evaluated in terms of existing data, and new experimental predictions to be generated on the basis of the existing structure of the model.

The physiological properties of the model have been analyzed with regard to experimental phenomena such as the size of place fields and the firing of units relative to theta rhythm. A measure of the size of place fields is shown in Figure 9. This demonstrates the difference in place field for simulated neurons in entorhinal cortex layer III and region CA1 of the simulation. As can be seen from the figure, the simulated place fields in layer III are considerably larger than the simulated place fields in region CA1.

FIGURE 9 ABOUT HERE

The activity of the network has also been analyzed in terms of the firing of neurons relative to theta rhythm. In experimental data, place cells often show a phenomenon termed theta phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996). When a rat first enters the place field of a place cell, the cell tends to fire at late phases of the theta rhythm. Then, as the animal gradually crosses the place field, the cell fires at earlier phases of the theta rhythm. This basic effect appears to be stronger for the latter half of the theta cycle (180 to 360 degrees), corresponding to the earlier part of the place field (Aota et al., 2001; Mehta et al., 2000, 2001). As shown in Figure 10, the spiking of neurons in the simulation shows properties similar to phase precession. On the Y axis, this graph plots the firing of the place cell relative to the phase of the ongoing theta rhythm oscillation. The position of the rat at the time of the firing is plotted on the X axis. Predictive firing appears at later phases of theta (upper left) when the rat is first entering the place field of a region CA1 place cell. This corresponds to activity driven by the retrieval activity in region CA3. Then as the virtual rat moves further into the place field, this predictive firing does not occur, and firing appears at earlier phases of theta (lower right) dependent upon direct input from EC layer III, bearing information about the current location. The simulation suggests that the biphasic nature of theta phase precession observed in experimental data arises from separate phases of predictive retrieval (late phases of theta) and encoding driven by current sensory input (early phases of theta). Previous models of theta phase precession have suggested that it may arise from the retrieval of encoded sequences (Tsodyks et al., 1996; Jensen and Lisman, 1996a; Wallenstein and Hasselmo, 1997), but this simulation places the precession in a specific functional context.

FIGURE 10 ABOUT HERE

In addition to showing the basic effect of theta phase precession, the network predicts an additional feature of precession which has not been analyzed. Specifically, it suggests that as the animal approaches the goal location, the phase of the predictive firing within the theta cycle should be reduced, as shown in Figure 10. Thus, cells should fire across a broader range of the theta cycle when they encode locations more distant from the goal location.

GENERALIZATION TO RULE LEARNING IN CORTICAL STRUCTURES.

The spatial navigation function described here uses dynamical interactions to select the pathway to a goal. Working memory for a specific goal causes activity to spread backward along multiple possible pathways to that goal. This interacts with forward spread from the current location to allow selection of the appropriate movement for approaching the goal.

This basic mechanism could be generalized to a broader set of behavioral problems which do not specifically involve pathways in space. If we consider the formation of representations of individual events in a sequence, the same basic framework could be used for goal directed behavior in operant tasks, and for the learning of rules.

A hypothetical network for neocortical function is shown in Figure 11. This network contains four primary populations of neurons.

1. An input population conveys information about the sensory environment and proprioceptive feedback from movements. This input converges on transent units at the same time as input from sustained units representing appropriate context.
2. An output population guides movements within the environment based on the activity of transient units.
3. A sustained population holds activity about previous inputs with repetitive spiking at slow intervals. This provides working memory of both goal activity and prior context, which converges with input to activate appropriate transient units. These sustained units are already active at the start of the task.
4. A transient population receives input from the sustained populations as well as from the input population, responding to convergent feedback from the goal and current sensory input to guide the next appropriate movement for performing the rule, and to activate other sustained units representing next context.

FIGURE 11 ABOUT HERE.

As an example of the process of rule learning, consider an alternation task (Wood et al., 2000), where food is available in one arm of a T maze, the rat runs down a diagonal return arm to the stem, and food is subsequently available in the opposite arm of the T-maze. The rat must learn to make a turning choice the opposite of its previous choice.

The connectivity of this network starts with random links between different layers which will select individual units during initial encoding. The network starts with active sustained units representing initial context. The starting sensory input converges with this context input to

activate a set of transient units. These transient units activate a random set of motor units (based on random subthreshold depolarization). In this manner, random exploratory movement can be generated through the environment. The sequential activation of the transient units and motor units cause strengthening of connections so that in future the convergence of a similar context on those transient units will drive the same motor outputs (what was random becomes driven by specific context and sensory input). Subsequently, each new context will converge with current sensory input to trigger a new motor output which will become associated with that context. In addition, backward links between the transient units will become strengthened (dotted lines in Figure 12). The connections developed in this process are summarized in Figure 12.

FIGURE 12 ABOUT HERE.

The random exploration can result in a number of different sequences of activity, but only the appropriate sequence resulting in encountering the goal will be retrieved, because activity will only spread along pathways associated with the goal. For example in the spatial alternation task, when the animal generates the sequence return from right, go straight up stem, turn left, it will encounter a food reward in the left arm of the T-maze. The consumption of the food will activate input from the ventral tegmental area which causes activation of the reward sustained units (ate food). These sustained units will hold their activity in a persistent manner for guiding subsequent movement. This activity spreads backward through the network, but will not guide the current activity if it does not yet converge with current sensory input. Thus, the rat might continue to generate random motor outputs until the current sensory input resembles sensory input which previously preceded the encounter with the goal.

When the sensory input does resemble previous input, then it can partially activate previously active sensory units, and previously active context units. Now there is a potential for this input activity to converge with the feedback from goal to activate specific transient units which cause spiking in motor units through previously strengthened connections. For example, this might happen the next time the rat reaches the stem of the maze. Now the subsequent actions can be determined by the convergence of feedback from goal with current sensory input. At each step the motor output results in the next predicted sensory input, but if the rat makes a left turn, it will not encounter the predicted food reward. (Because it repeated a turn choice rather than performing an alternation). In this case, the overlapping portions of the context representations will NOT form associations with the food reward representation. This will decrease the likelihood that this incorrect behavior will be generated in the future (but the link between context representations in the old sequence will not be weakened).

On a subsequent trial, the rat may make a correct choice in the sequence, choosing to turn right after returning from the left arm. In this case, activity will not overlap with prior context, and new representations will be formed. Because it made the correct choice of spatial alternation, it will encounter the food reward, and the network will have a new food reward representation activated in the sustained layer. This new goal representation will continue to be active subsequently. On additional trials, the rat will have goal activity spreading back along two feedback pathways. The subtle differences in context representations for returning from a left arm versus returning from the right arm should now

have the potential for influencing the choice. In this manner, the network will respond to the stronger feedback link with a correct response, and the elements of context shared between the two choices will have a weaker and weaker influence as new context units are activated on subsequent trials. If weights are normalized, older weights will become weaker as new context units are activated and new weights are strengthened along the feedback connections. In this manner, the network will gradually develop non-overlapping context representations for the shared portion of the pathway (the stem of the T-maze). These non-overlapping context representations could correspond to neurons which have been detected experimentally in the T-maze spatial alternation task. In that task, a large percentage of neurons respond on the basis of the past or future choice of the rat (Wood et al., 2000), suggesting development of separate neural representations for the distinct trial types alternating in the task.

True rule learning will require the ability to generalize specific responses to different sensory inputs. In the case of spatial alternation, the network takes different individual trials and picks up the essential feature of the nature of prior response. Thus, individual trials are linked to the correct goal activity by prior response. However, other rule based behavior requires generalization to many different sensory features. For example, a matching task requires that the "matching" rule be applied to multiple different sensory stimuli (Wallis et al., 2001) In these conditions, the network may obtain flexible application of the rule by analogy with initial correct matching responses. New stimuli will share the context of being presented at the same phase of the experiment. Sustained activity in these context units can hold the link to the new sensory input, to serve as a marker for which sensory stimulus was the sample on a given trial. This sustained units representing the link will then interact with feedback spreading from the goal to generate the correct match response on future trials.

CONCLUSIONS

The research presented here demonstrates potential theoretical mechanisms for the role of parahippocampal and hippocampal circuits in guiding spatial behavior. The use of a neural simulation interacting with a virtual rat in a virtual environment provides a useful perspective on potential problems and physiologically realistic solutions to these problems. The use of a network with spiking neurons allows analysis of the activity in the network in a manner similar to that used for experimental data, including comparison of place field size, and simulation of theta phase precession. Implementation of rule learning mechanisms will allow testing of potential mechanisms for development of separate neural representations of context on different trials in the spatial alternation task.

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FIGURE LEGENDS

FIGURE 1 - The T-maze reversal task. Initial training: Food reward is placed in the left arm of the maze, and the rat learns to retrieve food consistently from that arm over multiple trials. Errors after Reversal: Food reward is placed in the right arm of the maze, but rats continue to visit the initially learned location. Correct response: Rats explore the right arm and find the food reward. Choice: On subsequent trials, rats must choose on the basis of the recently learned location, rather than the strongly learned initial location.

FIGURE 2 - Diagram showing interaction of T-maze with simulation.
The essential components of the network simulation are summarized here. Input from a place representation ("place") depend upon the location of the virtual rat in the virtual environment. This input activates entorhinal cortex layer II, which has intrinsic properties allowing self-sustained activity, and sends excitatory output to entorhinal cortex layer III and region CA3. The input to CA3 can arrive directly or via the dentate gyrus (which has not yet been incorporated into the simulation). Region CA3 and entorhinal cortex layer III send converging input to region CA1. The place representation also sends subthreshold input to a region representing prefrontal cortex. Sensory input for proximity to objects ("proxim") activates a unit representing activation of ventral tegmental area by food reward. The input from ventral tegmental area enters the a prefrontal region along with input representing space. The convergence of ventral tegmental and place input to prefrontal cortex causes spiking and activation of intrinsic mechanisms maintaining working memory for reward location. During retrieval phases, the convergence of activity from entorhinal cortex layer III and region CA3 causes spiking in region CA1 indicating the appropriate next location. This spiking output guides the movements of the virtual rat toward the desired goal.

FIGURE 3 - Self-sustained spiking activity of simulated entorhinal neuron (Fransen et al., 2002). Top traces show membrane potential during suprathreshold stimulation. Bottom traces show response to subthreshold stimulation. In each of the four traces, the simulated neuron receives a depolarizing pulse representing sensory input, followed by a 2.6 second delay period ending with another depolarizing pulse. LEFT: Simulation of high acetylcholine levels. Acetylcholine activates the NCM current in the neuron, which is a calcium-sensitive inward current. The spikes elicited by the first depolarizing pulse cause influx of calcium through voltage-sensitive channels. The increase in intracellular calcium acctivates the NCM current more, causing further depolarization which causes additional spiking after the end of the depolarizing pulse. This causes another spike which causes further influx and further activation of spiking, allowing regenerative maintenance of activity during the delay period. RIGHT: With low acetylcholine levels, there is no activation of the NCM current. The neuron responds to depolarizing sensory input, but does not show delay activity or match enhancement.

FIGURE 4. Membrane potentials of two entorhinal neurons performing buffer function. As the rat explores the maze, this causes synaptic activation of the first neuron which spikes three times on one phase of subthreshold theta frequency oscillations. The second and third spike result from intrinsic calcium-sensitive cation currents (Fransen et al., 2002) which are

modeled with dual exponential functions. These currents cause the cell to spike at set intervals until a third spike occurs only a short time before the first spike of the next place cell (which also spikes three times). The interval between the last spike of the first cell and the first spike of the second cell is sufficiently brief to fall within the window of induction of long-term potentiation.

FIGURE 5 – Pattern of connectivity within region CA3 of the simulation. Lines represent excitatory connections between CA3 pyramidal cells which have been strengthened as the virtual rat explores the T-maze environment. Connections in opposite directions are offset from one another to illustrate the strengthened connections are bidirectional in this simulation, though larger scale simulations should be able to function with unidirectional connections. LEFT. Good encoding. As the rat explores the T-maze environment, sequential spiking of place cell representations is induced in EC layer III and region CA3. When encoding of sequential input from entorhinal cortex occurs at separate phases from the retrieval activity spreading along recurrent connections in CA3, then the network forms an effective representation of the T-maze, with connections (black lines) only between place cells representing adjacent locations in the maze. Note that the bidirectional exploration of the maze allows bidirectional strengthening of connections. RIGHT. Interference during encoding. Pattern of connectivity in the network when retrieval occurs during the encoding process. The spread of activity across previously modified synapses during encoding allows simultaneous spiking activity in neurons representing non-adjacent locations, and the buildup of this interference results in a pattern of connectivity between place cells representing locations which are not adjacent, and prevents accurate navigation of the virtual rat within the virtual environment.

FIGURE 6. - Schematic representation of the change in dynamics during hippocampal theta rhythm oscillations. LEFT: appropriate dynamics for encoding. At the trough of the theta rhythm in the EEG recorded at the hippocampal fissure, synaptic transmission arising from entorhinal cortex is strong. Synaptic transmission arising from region CA3 is weak, but these same synapses show a strong capacity for long-term potentiation. This allows the afferent input from entorhinal cortex to set patterns to be encoded, while preventing interference from previously encoded patterns on the excitatory synapses arising from region CA3. RIGHT: appropriate dynamics for retrieval. At the peak of the theta rhythm, synaptic transmission arising from entorhinal cortex is relatively weak (though strong enough to provide retrieval cues). In contrast, the synaptic transmission arising from region CA3 is strong, allowing effective retrieval of previously encoded sequences. At this phase, synapses undergo depotentiation rather than LTP, preventing further encoding of retrieval activity and allowing forgetting of incorrect retrieval.

FIGURE 7 - Performance of the network depends on the relative phase of oscillations in synaptic transmission and long-term potentiation (Hasselmo et al., 2002). This graph shows how performance in T-maze reversal changes as a function of the phase difference between LTP and synaptic input from entorhinal cortex (EC phase) and of the phase difference between LTP and synaptic input from region CA3 (CA3 phase). Mathematical analysis

(Hasselmo et al., 2002) shows how function depends on phase relationships between variables in the following manner:

$$M = (X/2)\pi \cos(\phi_{LTP} - \phi_{EC}) - K - (X/2)\pi \cos(\phi_{LTP} - \phi_{CA3})$$

Best performance occurs when EC input is in phase (zero degrees) with LTP, but when region CA3 synaptic input is 180 degrees out of phase with LTP.

FIGURE 8
Network activity during goal directed navigation. Each rectangle shows the activity within a specific simulated region, with time plotted horizontally and individual neurons plotted vertically. Individual spikes appear as black rectangles. On the left, a schematic of the T-maze shows how the activity of cells in the simulation corresponds to mental representations of the environment. In EC layer III (top), input from prefrontal cortex induces a spike at the goal location, and spiking spreads back from goal location through neurons representing adjacent locations into neurons representing the stem and right arm of the maze. When this activity reaches the current location, it causes spiking in EC layer II (not shown) which induces a spike in the place cell representing current location in CA3 (bottom). Spiking activity in CA3 spreads forward one step from current location before feedback inhibition shuts it off. The spiking activity in CA3 and EC layer III converges on region CA1, where it causes spiking in a neuron representing the next desired location. The virtual rat then moves to this next desired location. These mechanisms allow selection of the next step along the shortest pathway to the closest goal.

FIGURE 9
Size of place fields. Each dot represents the location of the virtual rat when a spike was fired by an individual simulated neuron in region CA1 (LEFT) or entorhinal cortex (RIGHT). Note that the broader spread of activity in entorhinal cortex causes larger place fields in EC versus CA1, consistent with experimental data (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000).

FIGURE 10
Plotting of the spike times of a simulated place cell relative to phase of the theta rhythm and position of the virtual rat. This demonstrates a phenomena resembling the experimental phenomenon of theta phase precession. The spike times of the simulate place cell is plotted in the same format used for analyzing theta phase precession in experimental data (Skaggs et al., 1996). Individual spike times are plotted as black dots relative to two dimensions. The X-axis shows the linear position of the virtual rat at the time of the spike relative to the path from the start of the stem to the reward location in the left arm. The Y-axis shows the time of the spike relative to the phase of theta rhythm oscillations of the entorhinal input. The simulated place cells show predictive firing for next desired location in the late phases of theta (before they move to this position). These dots appear in the upper left. The firing is driven by direct sensory input at the time the neurons enter the position (during early phases of theta). These spikes appear in the lower right.

FIGURE 11
Potential circuit for rule learning in spatial alternation task. The neural circuit starts with sustained activity in units holding activity representing previous context and desired goal. This sustained activity interacts with input to activate transient units in a separate layer which send motor output to guide the appropriate action at the appropriate time (in this case a left turn) and to update the sustained unit context. Sensory input about the actions (in this case, went left) enters the circuit through separate input units which activate transient units for the next step. These transient units activate new sustained units to provide context for future changes in activity.

FIGURE 12
Network interactions which could mediate performance of spatial alternation rule. After experiencing all the stages of the task, the network holds rule activity (Ate food) due to modulatory input during food consumption. This active sustained unit activates the corresponding transient unit, and activity spreads backward (along dotted lines) through transient units representing preceding events. This activity does not cause output until it interacts with the current sensory input (stem after right). The convergence of current sensory input and feedback from goal activates the appropriate next motor output (turn left).

Figure 1

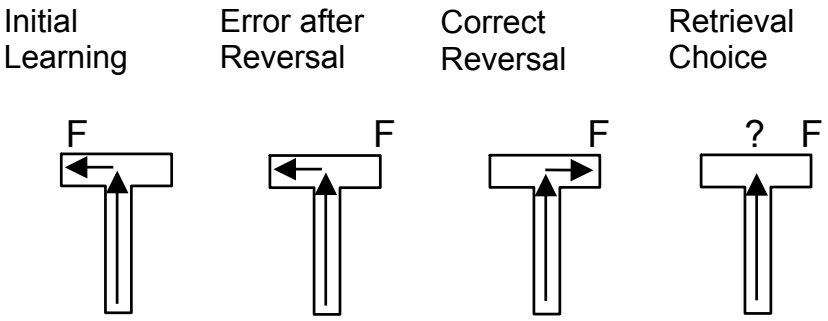

Initial Learning
Error after Reversal
Correct Reversal
Retrieval Choice
F
F
F
? F

Figure 2

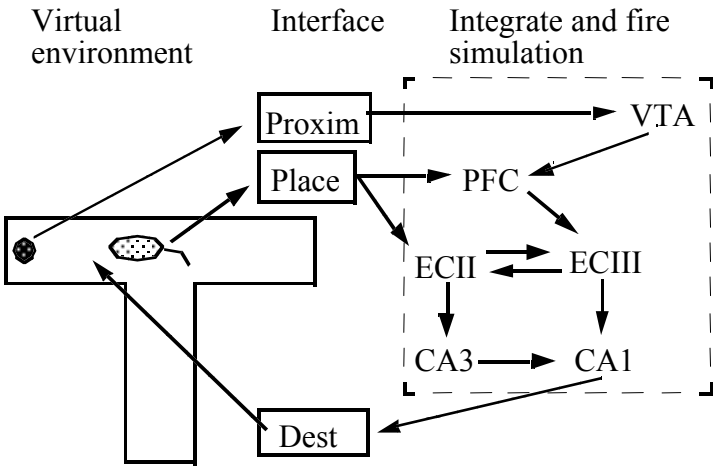

Virtual environment
Interface
Integrate and fire simulation
Proxim
Place
Dest
VTA
PFC
ECII
ECIII
CA3
CA1

Figure 3

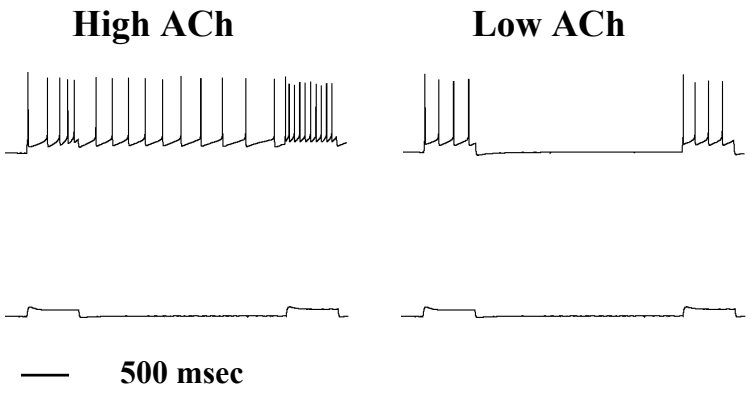


Figure 4

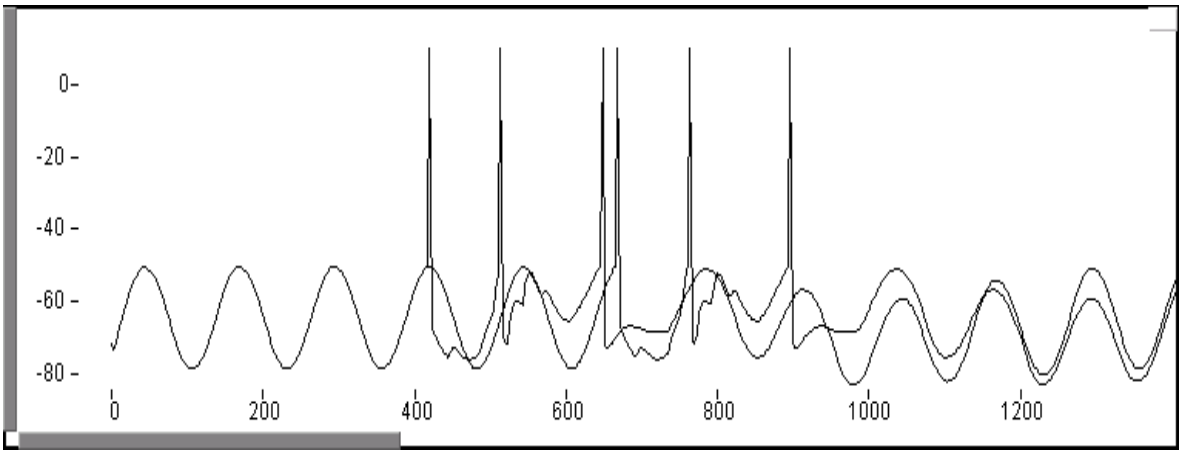


Figure 5

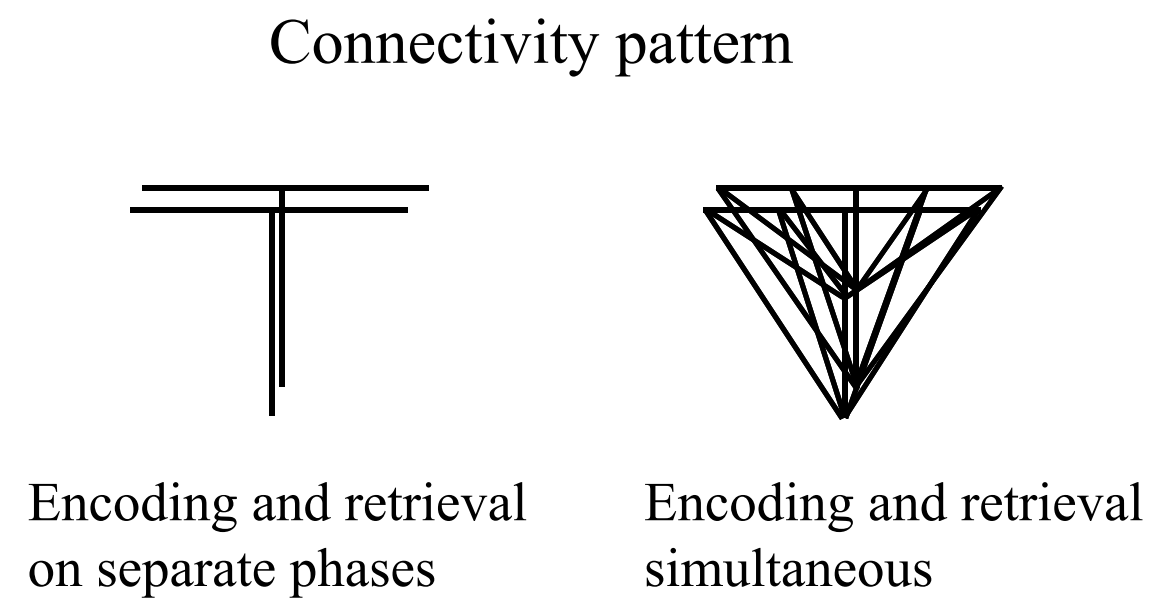

Connectivity pattern
Encoding and retrieval on separate phases
Encoding and retrieval simultaneous

Figure 6

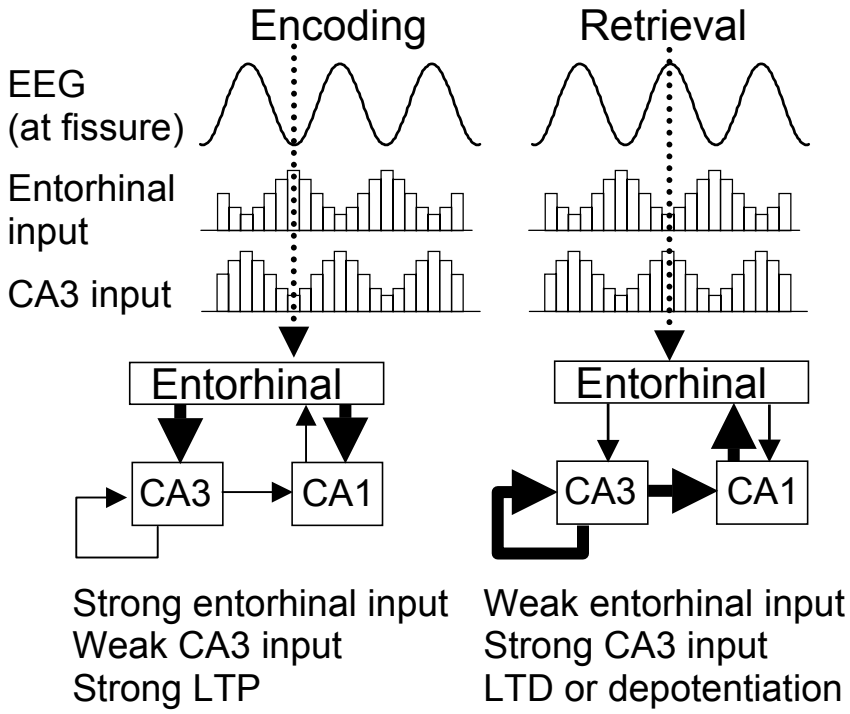

Encoding
Retrieval
EEG
(at fissure)
Entorhinal
input
CA3 input
Entorhinal
Entorhinal
CA3
CA1
CA3
CA1
Strong entorhinal input
Weak CA3 input
Strong LTP
Weak entorhinal input
Strong CA3 input
LTD or depotentiation

Figure 7

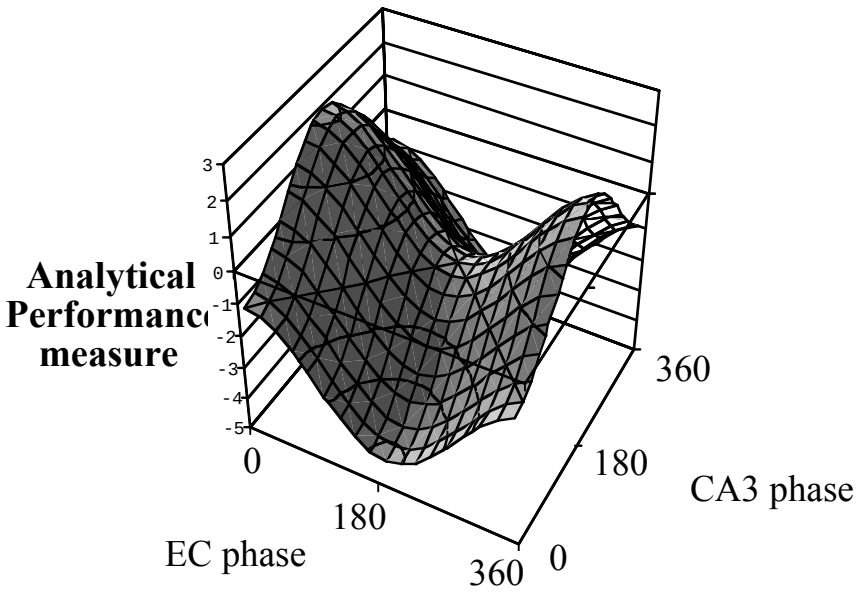

Analytical
Performanc
measure
3
2
1
0
-1
-2
-3
-4
-5
0
180
360
EC phase
0
180
360
CA3 phase

Figure 8

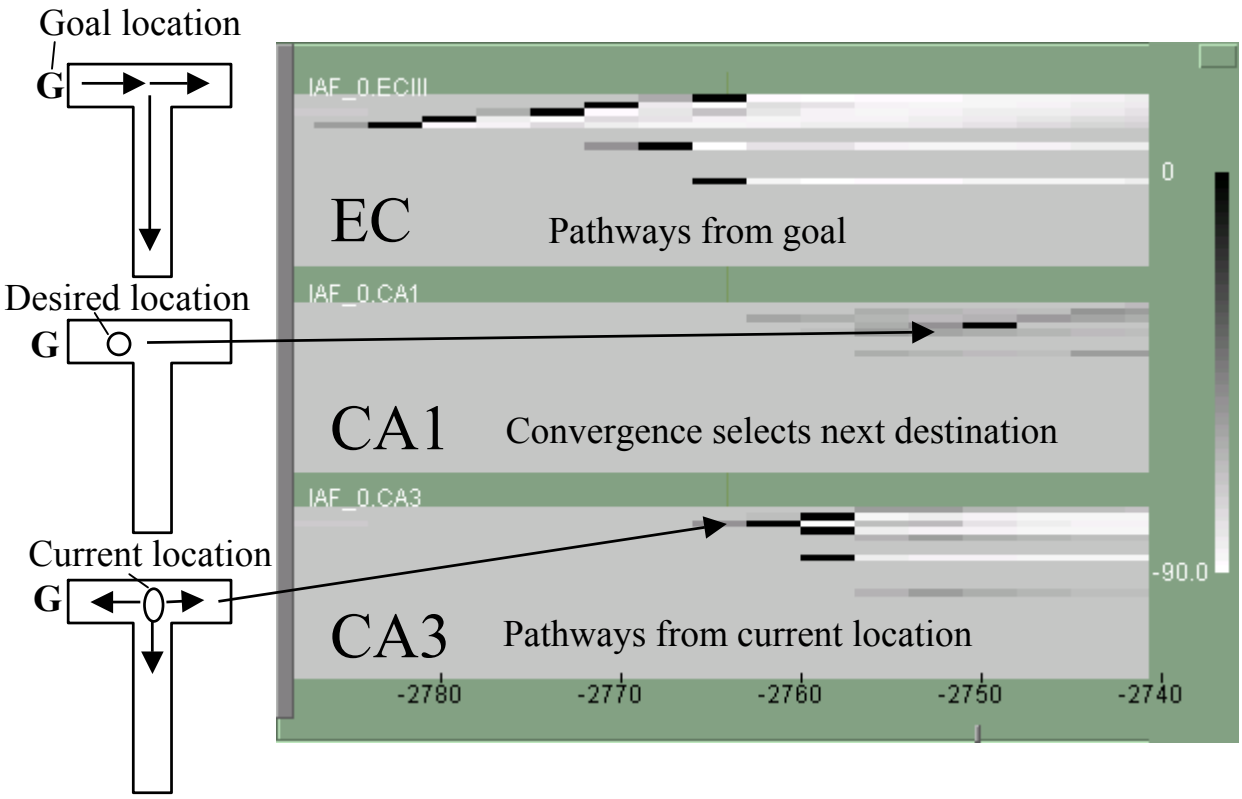
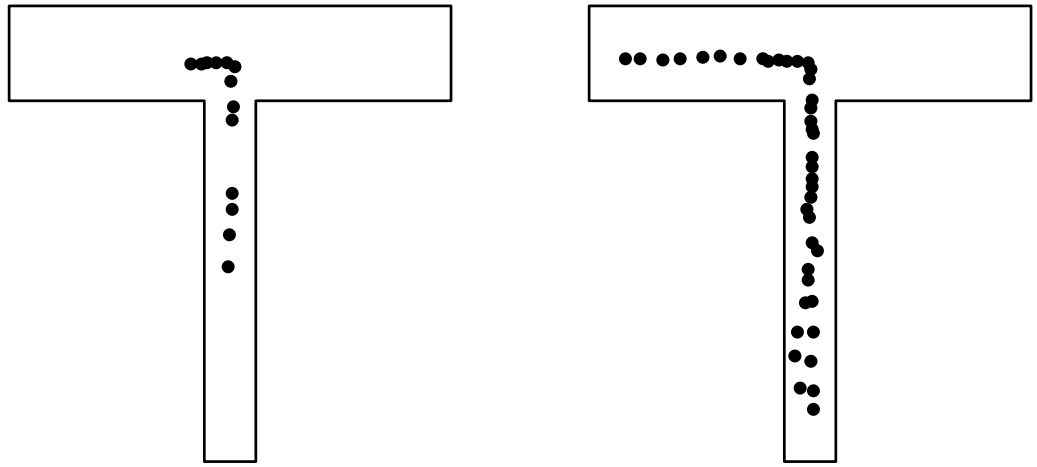

Goal location
G
Desired location
G
Current location
G
IAF_0.ECIII
EC
Pathways from goal
IAF_0.CA1
CA1
Convergence selects next destination
IAF_0.CA3
CA3
Pathways from current location
0
-90.0
-2780
-2770
-2760
-2750
-2740

Figure 9



Region CA1 neuron Entorhinal cortex

Figure 10

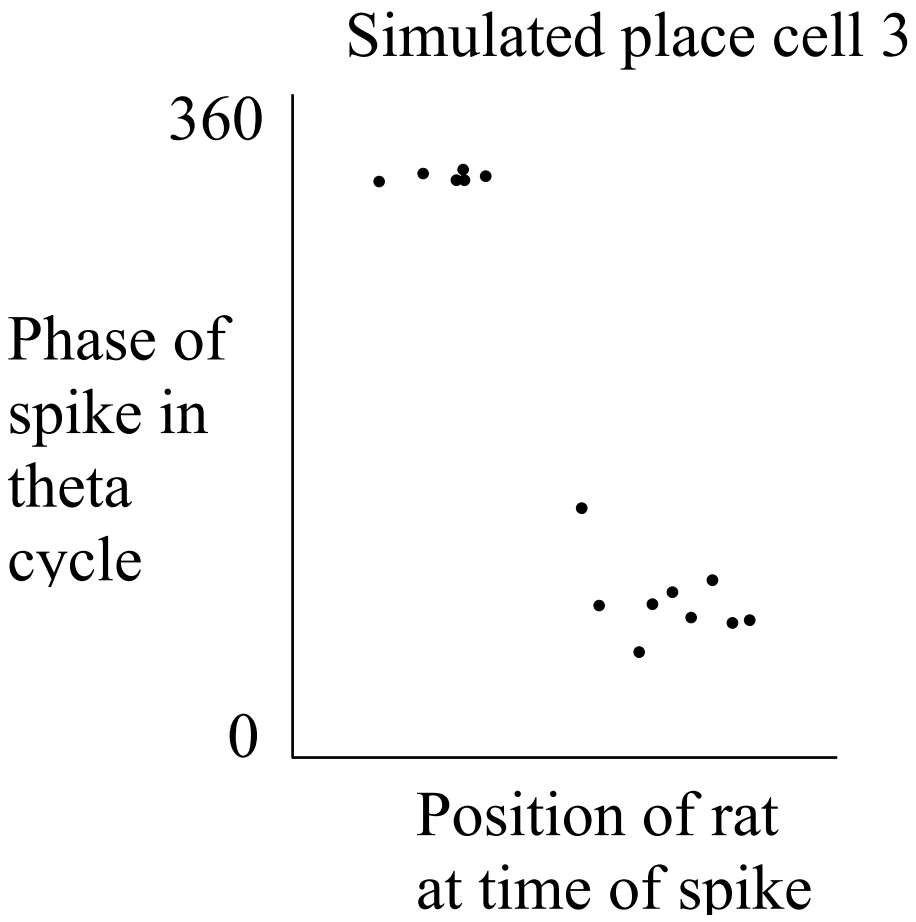

Simulated place cell 3
360
Phase of spike in theta cycle
0
Position of rat at time of spike

Figure 11

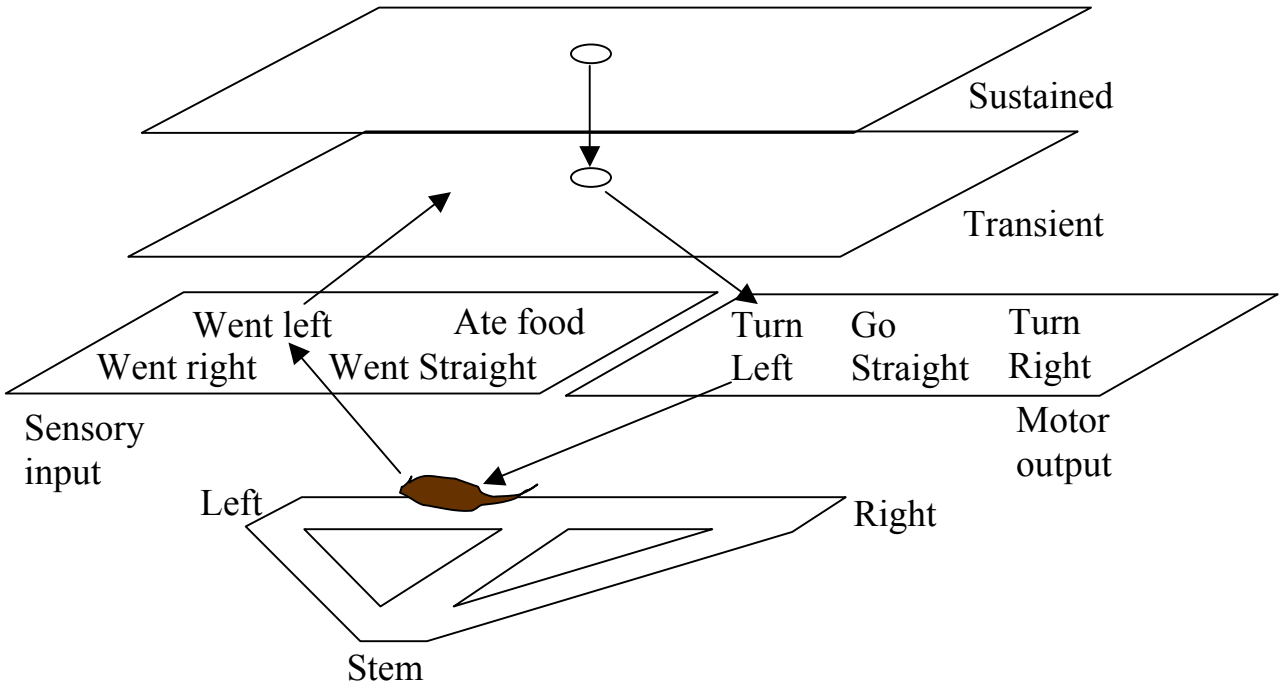
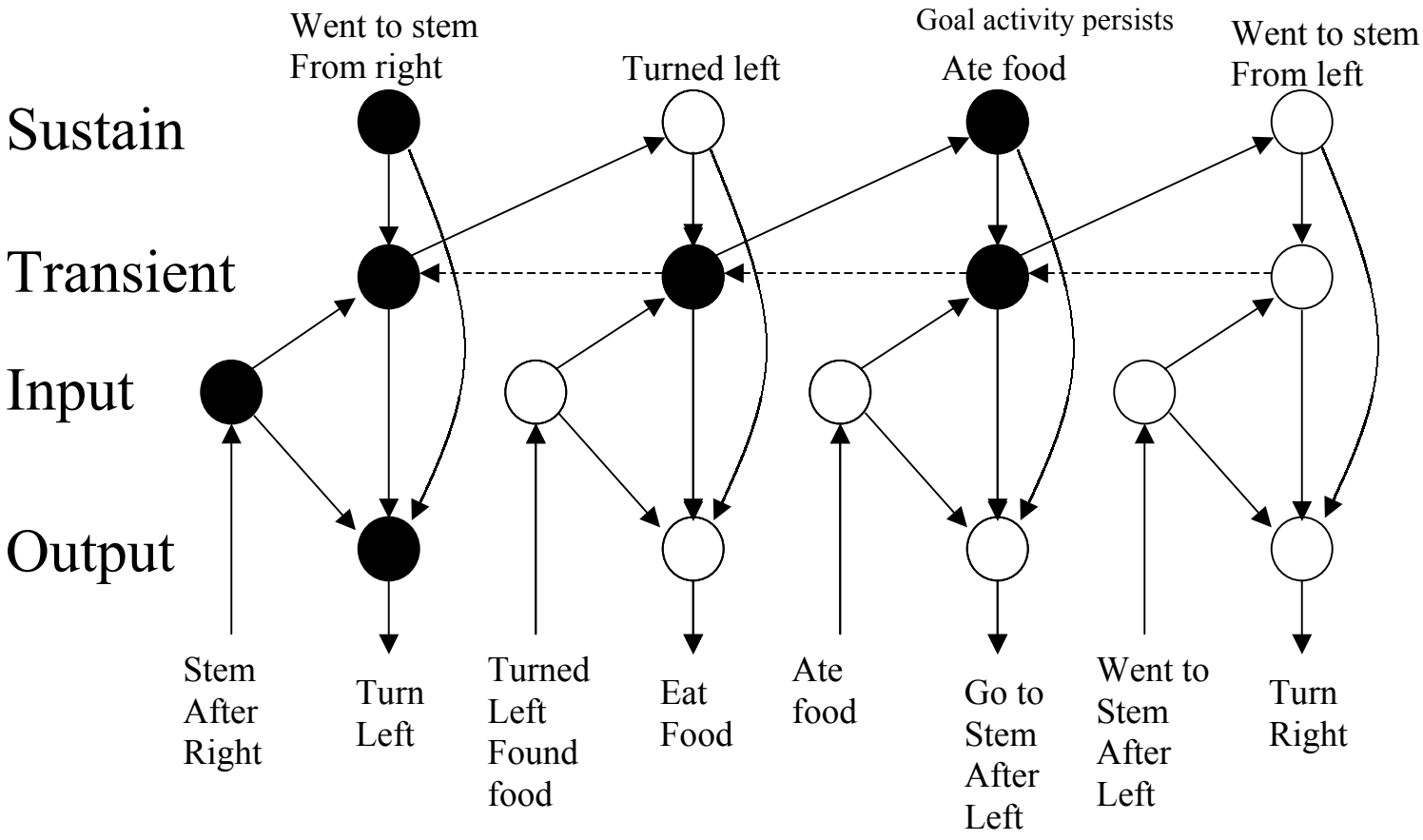

Sustained
Transient
Went left
Ate food
Went right
Went Straight
Turn
Left
Go
Straight
Turn
Right
Sensory
input
Motor
output
Left
Right
Stem

Figure 12


Went to stem
From right
Turned left
Goal activity persists
Ate food
Went to stem
From left
Sustain
Transient
Input
Output
Stem
After
Right
Turn
Left
Turned
Left
Found
food
Eat
Food
Ate
food
Go to
Stem
After
Left
Went to
Stem
After
Left
Turn
Right