

Role of the dual entorhinal inputs to hippocampus: a hypothesis based on cue/action (non-self/self) couplets

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Abstract: The hippocampus sits at the highest level of memory processing circuits and receives two major inputs, one coming from the lateral entorhinal cortex and one coming from the medial entorhinal cortex. This duality must be of fundamental importance, but its functional meaning remains unclear. A computational model used for robot navigation (Verschure, P.F., et al. (2003). *Nature*, 425: 620–624) has a dual information structure that may provide insight. In this model, information is stored as couplets consisting of information about the current sensory cues and information about the current action of the robot. Sequences of such couplets are stored in a short-term memory buffer and transferred to a long-term memory store whenever a goal is found. The overall system enhances the ability of the robot to find reward sites because stored sequences enable the robot to retrace the path to a goal site whenever any of the cues along the path to a goal is subsequently encountered. A review of the literature suggests that the idea of cue/action couplets can be usefully mapped onto the function of the entorhinal cortex. Cue information may be supplied by the lateral entorhinal cortex whereas action (motor) information may be supplied by the medial entorhinal cortex. However, given that self-position information is prominent in the medial pathway and that this is not directly related to action, a modified formulation of the duality is proposed in which the fundamental distinction is between information about non-self vs. information about self. According to this view, the lateral entorhinal pathway carries information about external (non-self) cues and their positions (in egocentric coordinates) whereas the medial entorhinal pathway carries information about the organism itself, including its position (in allocentric coordinates), motor actions and goals.

Keywords: short-term memory; reward; navigation; sequence memory; dopamine

Overview

The duality (Fig. 1) of the connections from the entorhinal cortex to the hippocampus is anatomically striking (Burwell et al., 1995). The entorhinal cortex contains two distinct regions, the lateral

and medial regions. These provide excitatory input to several parts of the hippocampus, but the duality of their structure is most obvious in the dentate gyrus. The outermost dendritic region of dentate granule cells receives exclusive input from the lateral entorhinal cortex whereas the middle dendritic region receives exclusive input from the medial entorhinal cortex. Each granule cell receives both types of inputs, thereby integrating the

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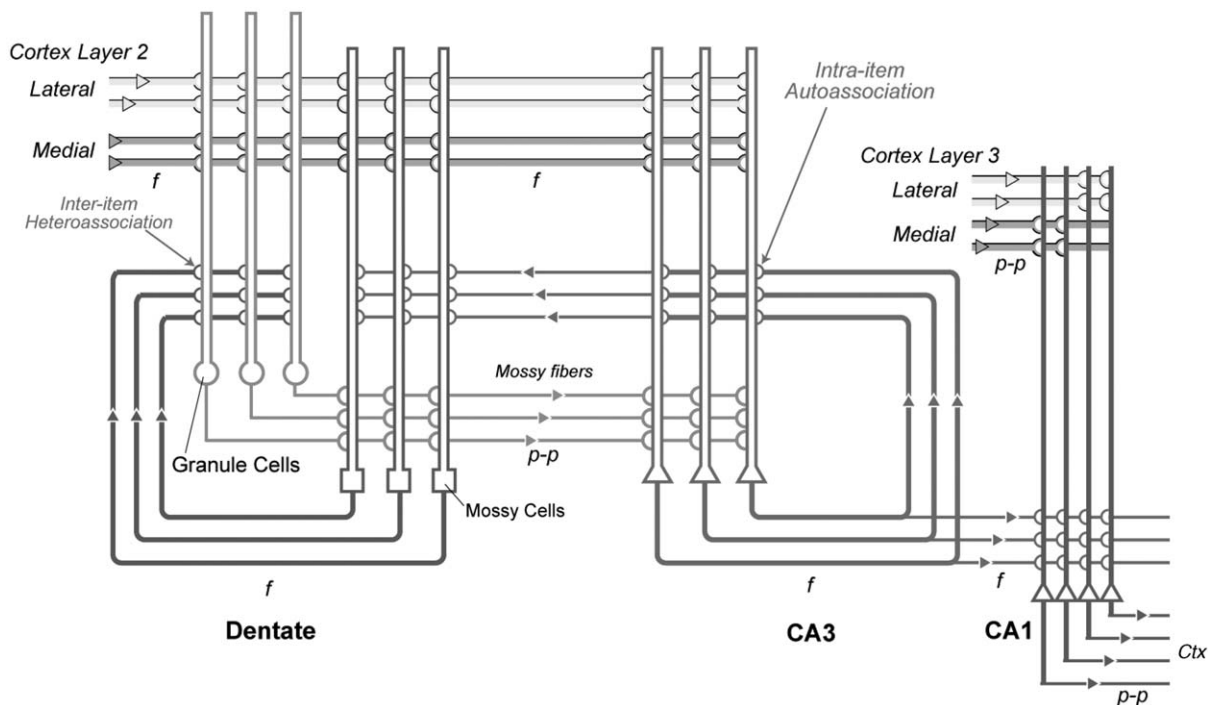


Fig. 1. Wiring diagram of the hippocampus (interneurons excluded) showing dual inputs from the lateral and medial entorhinal cortex. The layer 2 cortical inputs to the dentate and CA3 diverge fan out (*f*) widely over these networks and then provide convergent input to individual dentate granule cells. In contrast, the layer 3 cortical inputs are specialized for individual subregions of CA1. This is an example of a point-to-point (*p-p*) connection. Within the hippocampus, granule cells provide input, via mossy fibers to the mossy cells of the dentate and to CA3 cells. CA3 cells make feedback connections to themselves and to the mossy cells of the dentate. These, in turn, provide excitatory input to granule cells in the inner third of the granule cell dendritic tree. (See Color Plate 33.1 in color plate section.)

two lines of cortical information. The purpose of this review is to discuss the possible functional basis of this mysterious duality.

A priori, what are the grand dualities that might be considered? Here is a list of some possibilities: what/where; specific/context; sensory/motor; past/present; conscious/unconscious; rewarded/punished; stimulus/response.

My interest in the last of these, stimulus/response, was stimulated by a paper on robotic control (Verschure et al., 2003). In that paper, the authors describe a “brain-like” computer program that enables a robot to efficiently find sites at which reward is located. The authors postulated several levels of control. At the lowest levels, circuits support classical conditioning. In this way, the robot learns to associate a previously neutral stimulus with a reward that is close to the robot.

But the robot becomes much more efficient at finding reward sites if there are additional circuits. These make it possible for a cue that is far away from a reward site to specify a complex path that, according to previous experience, led to the reward site. The circuitry that allows the robot to do this (Fig. 2) involves a “cortical” multi-item “circular” short-term memory (STM) buffer that stores the last five salient events, and a long-term “hippocampal” memory that stores sequences of events in long-term memory (LTM). When the robot forages and accidentally finds a reward, it incorporates the entire content of the buffer into its LTM store. Importantly, each event is defined as a stimulus/response couplet (Verschure and Voegtlin, 1998; Verschure et al., 2003). The “stimulus” part of the couplet corresponds to a prototype of the sensations from the external world at a particular

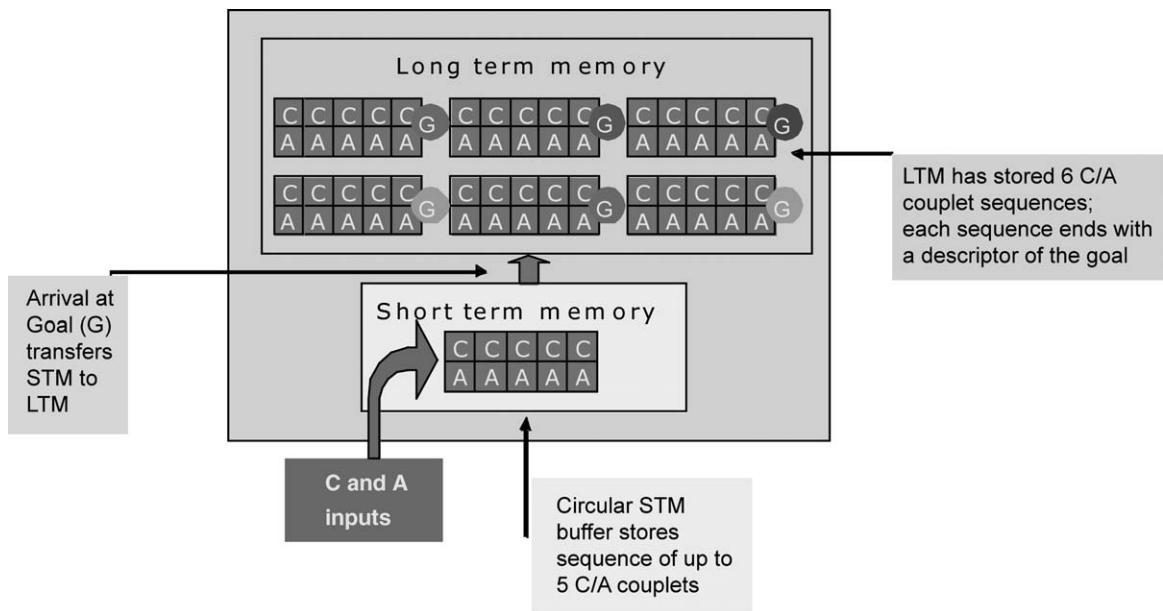


Fig. 2. Diagram of circuits responsible for storing events that led to the discovery of goals according to the model of [Verschure et al. \(2003\)](#). Stimulus (C) and motor action (A) for each event are stored in a circular (first in, first out) short-term memory buffer. This multi-item buffer can store five C/A couplets. When a goal is reached, the sequence in the short-term memory buffer is transferred to the long-term memory buffer together with a last item representing the goal (G). As illustrated, the long-term memory store has stored six sequences.

location. The response part of the couplet corresponds to the motor act that was executed to get from that cue to the next location (cue) in the sequence. “Stimulus” and “response” have a particular meaning in classical conditioning that is not appropriate in the current context; I will therefore use the terminology *cue/action* (C/A) to describe a couplet. Thus the utilization of stored couplets can be described as follows. If the robot comes across a previously encountered cue, C_n , it can get to the reward site using a simple algorithm: execute the action A_n , that is associated with C_n in LTM; when C_{n+1} is found, execute A_{n+1} , etc.

Several comments are in order. First, [Verschure](#) (personal communication) was not aware of the dual inputs to the hippocampus; the dual representation was utilized simply because it enhanced the robot’s efficiency at finding goals. Second the use of a sequence of cue-driven actions to find a goal site is an experimentally observed mode of animal navigation ([Collett et al., 2003](#)) and is related to ideas incorporated into previous reinforcement driven models of behavior ([Barto and](#)

[Sutton, 1981](#); [Hasselmo, 2005](#)). This form of navigation is less flexible than map-based navigation, which may have developed later in the evolution. Importantly, the use of C/A sequences to specify the route to an accidentally discovered reward site absolutely relies on one-trial learning, a property that remains a defining property of human hippocampal episodic memory. Indeed, the development of a multi-item STM buffer may have been the crucial evolutionary change that made one-trial learning possible rather than a change in synaptic plasticity mechanisms themselves. This is because such buffers capture one-trial, brief events and then, upon command, provide the *repetitive* activity patterns to LTM networks that are necessary to produce stable synaptic modifications.

In the following sections I will address two questions:

1. Is the idea of storing C/A couplets potentially applicable to understanding the dual cortical inputs to the hippocampus? In particular, is there any way of mapping this duality onto

the known properties of the medial and lateral entorhinal inputs to the hippocampus?

2. What is the status of the evidence for the various building blocks postulated in the model of Fig. 2?

Evaluation of the cue/action (C/A) couplet hypothesis

Evidence that the hippocampus receives action (motor) and cue (sensory) information

The idea that the hippocampus might be influenced by the motor system is one that is not commonly discussed, but support for this idea is actually quite long-standing. Vanderwolf (1969) observed that the frequency and amplitude of hippocampal theta oscillations is modulated by the speed of a rat [reviewed in Bland and Oddie (2001)]. Other work shows the influence of motor set and running speed on place cell firing (McNaughton et al., 1983; Foster et al., 1989; Wiener et al., 1989). Ranck (1973) found hippocampal neurons that fired on “approach” to objects. More recent work provides direct evidence that “motor intent” influences hippocampal function. Specifically, when rats run in a T-maze, the firing of neurons that occurs when the rat is in the vertical stem of the T can be different depending on which direction the rat will turn at the top of the stem (Frank et al., 2000; Wood et al., 2000; Bower et al., 2005). Because the sensory stimulation in the stem is always identical, it is hard to escape the conclusion that goals or action are what cause the difference in firing. It might be argued that what is represented is the goal, in some abstract sense not related to the motor action needed to get to goal, but this is not the case. In experiments using a plus maze, rats were started in the north or south arm and had to reach a goal in the east arm; when the rat reached the east arm, many cells fired differentially depending on whether the approach was from the north or south (Ferbinteanu and Shapiro, 2003). Thus, although a common goal was involved, information about the specific path taken was encoded. Recent results emphasize that pathway-specific firing may occur

only when the behavioral paradigm has consequences for reward (Smith and Mizumori, 2006). The influence of goals on hippocampal responses is not limited to rats, but is also evident in humans (Ekstrom et al., 2003).

There is also strong experimental support for the entry of sensory-specific information into the hippocampus. Odor-specific cells are found in the rat hippocampus (Wood et al., 1999), and neurons that are scene-dependent have been observed in monkey hippocampus (Wirth et al., 2003). Rat hippocampal neurons become sensitive to tones after aversive conditioning (Berger et al., 1976; Moita et al., 2003). Particularly clear evidence for cells responsive to particular faces has been obtained in humans (Quiroga et al., 2005).

It thus seems clear that both motor and sensory information can get to the hippocampus. Moreover, particularly important from the perspective of the hypothesis developed here is the finding of cells in both rat (Ranck, 1973) and monkey (Wirth et al., 2003) that jointly encode sensory and motor information. For instance, in the monkey work, particular pictures are rewarded for movements in a particular direction; as learning becomes apparent, some hippocampal neurons fire selectively when a particular picture is presented and the monkey performs the correct learned movement.

Evidence that the hippocampus is necessary for sensory/motor associations

An important series of experiments has addressed whether the hippocampus is necessary for learning the association between sensory cues and motor responses. It was found that lesions to the fornix, a major input/output tract of the hippocampus, prevent a monkey from learning which direction to move in response to a sensory cue (Rupniak and Gaffan, 1987), and interferes with the ability of a monkey to report the previous movement that it made (Gaffan, 1985). Recent work (Brasted et al., 2005) extends these observations by showing that fornix lesions prevent learning of arbitrary sensory/motor tasks in single trials, the fast learning that is required to enhance foraging (see above). Related work on instrumental conditioning in rats

demonstrates a similar requirement for hippocampal involvement (Corbit and Balleine, 2000).

Taken together, these observations indicate that hippocampal cells code for much more than position and are influenced by the goal and actions required to get there. Moreover, the association of these two types of information in the hippocampus appears necessary for behavioral responses based on this association. I now turn to the issue of which region of the entorhinal cortex supplies each type of information.

Sensory properties of the lateral entorhinal cortex

The perirhinal cortex, often termed inferotemporal cortex, is involved in high-level aspects of object recognition (Brown and Aggleton, 2001). This region provides strong input to the lateral entorhinal cortex, but little to the medial entorhinal (Burwell, 2000). Physiological evidence for sensory input to the lateral entorhinal cortex is its responsiveness to stimulation of olfactory cortex in rat (Gnatkovsky et al., 2004) and the presence of novelty-sensitive responses to visually presented objects in monkey (Fahy et al., 1993). Thus, the idea that the lateral perforant pathway is sensory driven has experimental support. Consistent with a sensory role, lesions of the hippocampal inputs from the lateral entorhinal cortex produces decreased investigation of novel objects (Myhrer, 1988).

Motor/goal properties of the medial entorhinal cortex

In contrast to the cells of the lateral entorhinal cortex, which do not have spatial properties (Hargreaves et al., 2005), layers 2 and 3 of the medial entorhinal cortex contain grid cells with robust spatial properties (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006). These cells are coded in an allocentric coordinate system (i.e. with respect to an absolute reference frame in the environment, as e.g. north/south). Consistent with the presence of such allocentric spatial information, lesions of the hippocampal inputs from the medial entorhinal (but not the lateral entorhinal cortex)

interfere with place learning (Ferbinteanu et al., 1999).

Validity of the C/A duality

In mapping the C/A duality onto the entorhinal cortex, we would have to suppose that the lateral region is sensory (cue) and that the medial region represents “action”. However, the most abundant cells in the medial region are grid cells, representing the position of the rat in the environment, and such information does not seem directly tied to action. At best one could argue that motor information may be used to compute position (McNaughton et al., 2006); the computation is not dramatically altered when important sensory cues, such as vision, are taken away, probably because a path integration mechanism can compute position using head direction and velocity information, both of which are motor-related. A significant number of layer 3 cells are direction-dependent, providing additional suggestive evidence that goal/motor information is present in the medial entorhinal cortex (Sargolini et al., 2006). Thus, to some extent, positional cells could be described as related to action, but this argument is not compelling.

Another major theory of the duality (what/where) also faces difficulties. If one views grid cells as primarily representing “where”, it at first seems sensible to conclude (Hargreaves et al., 2005) that the dual inputs to the hippocampus form a what/where couplet, not a C/A couplet. However, does the “where” in this formulation refer to the organism or to objects in the environment? The brain needs to keep track of both, and it is unclear how this would be done in the context of a what/where duality.

Cue/action as a special case of a non-self/self duality

To deal with these difficulties, I suggest a reformulation of the duality as non-self information vs. self-information. According to this view, the lateral entorhinal pathway would carry information about what is in the environment (non-self) and the “where” of those objects. The coding of the

“where” component would presumably be done in the *egocentric* (relative to the observer) coordinates of the parietal lobe. The medial entorhinal pathway would encode information about various aspects of self that includes a general specification of where one is in the environment (in *allocentric* coordinates — relative to a fixed map of the environment) and the action being taken towards achieving goals. Importantly, the allocentric coding evident in the medial entorhinal cortex could provide an excellent way of specifying directional action (e.g. turn North) because the correct action can be triggered by a cue approached from any direction. In contrast, egocentric specification (e.g. turn Right) would work only if the cue is approached from the same angle as during initial learning.

To give a specific example of how *non-self/self* information might be encoded by a *lateral/medial* entorhinal couplet, consider the following description of a moment in my morning commute. When I see the following *non-self information*: [*McDonald's and, to its right, Burger King (complex cue specified in egocentric coordinates)*], this would be coupled to the following *self information*: [*given that I am on my way to work (my goal), when I'm near Brandeis (my place approximated in allocentric coordinates), I turn West (my action in allocentric coordinates)*].

Parenthetically, one can see from this example that purely landmark-based navigation would fail if there are many similar landmarks, as is the case for fast food establishments, and that even a crude allocentric system (“near Brandeis”) can therefore be helpful in disambiguating landmark cues.

It would seem that the *non-self/self* formulation is a plausible one and fits the data somewhat better than the *C/A* formulation. In the final sections I will turn to the question of how this formulation might be tested.

Evidence for the building blocks required by the model (Fig. 2)

The general model of Verschure et al. requires several important building blocks: a circular, multi-item STM buffer, a LTM capable of holding couplet sequences, and a control system that would

transfer the buffer content to the LTM store when a reward site is found. I will now review what is known about the existence of such components.

Evidence for the circular multi-item STM buffer in cortex

A requirement of reward-dependent storage of long paths leading to the reward is the existence of a multi-item “circular” buffer. When the reward site is found, the contents of the buffer (the *C/A* sequences leading to the reward site) are transferred into the LTM store. The existence of a multi-item STM in humans has been deduced from psychophysical studies (Atkinson and Shiffrin, 1968). This buffer is thought to have limited capacity (7 ± 2 items) and to be “circular”. Here “circular” means that when the buffer is full, the next arriving item knocks out the item that has been in the buffer the longest (i.e. first in, first out). In the context of the model shown in Fig. 2, the circular property ensures that when the goal is reached, transfer of buffer information into LTM will incorporate information about the last five events that occurred before the goal was found.

A physiologically plausible model of a multi-item STM buffer has been developed (Lisman and Idiart, 1995) and a recent variant has first in, first out properties (Koene and Hasselmo, 2006). fMRI evidence points to the temporal lobe as a site of a multi-item working memory buffer, as evidenced by the load dependence of the fMRI signal (Fiebach et al., 2006). There is evidence that the entorhinal cortex can maintain STM information (Otto and Eichenbaum, 1992) [reviewed in Jensen and Lisman (2005); Hasselmo and Stern (2006)]. Recent experiments indicate that the persistent firing is due to a cholinergically enhanced intrinsic conductance that produces an after depolarization (Fransen et al., 2006), as postulated in the theoretical models (Lisman and Idiart, 1995).

Evidence for reward-mediated fixation of STM content into hippocampal LTM

It is generally thought that reward signaling is mediated by the dopaminergic cells of the ventral

tegmental area and substantia nigra. It was originally thought that dopamine did not affect the hippocampus, but recent work indicates that there is dopaminergic innervation of the hippocampus and that it can profoundly affect transmission and enhance LTP [reviewed in Lisman and Grace (2005)]. In the context of the model of Fig. 2, one might imagine that it is the dopamine reward signal that stimulates reward-dependent *transfer* of information from STM to LTM, but no experiments have addressed this directly, so not much can be said about this possibility at the present time. One relevant observation (Foster and Wilson, 2006) is that when rats reach a reward site, a replay of the sequence of events (places) that led the rat to the reward occurs in the hippocampus (the replay occurs in reverse order). Although it is suspected that this replay occurs as a result of processes within the hippocampus itself, the possibility that it actually occurs because of input from the cortex needs to be directly tested.

Although the role of dopamine in transfer, is uncertain, there is quite strong evidence that dopamine is necessary for the late stage of LTP (reviewed in Lisman and Grace, 2005). In this way, dopamine may contribute to the reward-dependent storage of sequences envisioned in Fig. 2.

Evidence for hippocampal LTM stores capable of storing sequences

There have been many computational models of the hippocampus (Burgess et al., 2001; Kunec et al., 2005; Rolls and Kesner, 2006), but most deal exclusively with autoassociational memories that encode events at a given moment, and so cannot be used to account for sequences of events. Models developed in my laboratory, which have been improved over time (Jensen and Lisman, 1996; Lisman, 1999; Lisman et al., 2005), deal with how the hippocampus can store and recall sequences (see also Levy (1996)). This class of models shows how gamma and theta oscillations, standard NMDA receptor-mediated plasticity processes and known anatomical connections (including the feedback connections from CA3 to dentate) can mediate

successful transfer of sequences from a multi-item cortical STM buffer to hippocampal LTM.

It may be instructive to consider how such processes might transfer *C/A* sequences from STM to LTM and later use the stored information to recall them. During learning, the elements of *C* from lateral entorhinal cortex and the elements of *A* from medial entorhinal cortex converge on subsets of granule cells; each granule cell that fires forms an element of the *C/A* representation. The output of active granule cells excites a subset of CA3 pyramidal cells, and these are combined into an associative representation of the *C/A* couplet by LTP in the recurrent connections of the active CA3 cells. The CA3 output is then sent back to the dentate, where the synapses onto granule cells representing elements of the next *C/A* couplet in the sequence become potentiated. These feedback synapses thus form linkages between sequential events. In this way, the entire sequence can be transferred from a cortical buffer to the hippocampal memory [see Lisman et al. (2005) for details]. Now let us assume that the organism subsequently comes across C_2 , and the corresponding input is supplied to the dentate, which then provides input to CA3. Through autoassociative memory of the stored couplet, the A_2 component of the couplet will be evoked. The completed C_2/A_2 couplet is sent back to the dentate, where it evokes the C_3/A_3 couplet (this is termed a *chaining* step). The vagaries of synaptic transmission will, however, lead to a slightly corrupted representation of the couplet, which, if used to chain to the next element, would lead to an even more corrupted version of C_4/A_4 . However, the reciprocal connections between the dentate and CA3 can serve to prevent such concatenation of errors (Lisman, 1999). Specifically, C_3A_3 sent to CA3 where the autoassociative properties of CA3 correct the errors in the C_3/A_3 representation and it is this corrected version that is sent from CA3 to the dentate, where it triggers C_4/A_4 . Thus, through sequential chaining and correction processes, the dentate and CA3 can lead to accurate recall of the entire sequence of couplets leading to a goal. Other brain circuits could then use this stored information to make a decision about whether this goal is worthwhile in the current context and, if so, to

execute the specific motor plans stored in the couplet sequence.

Although most computational models of the hippocampus posit that the sole function of the dentate is to produce orthogonalization (the generation of very different firing patterns to slightly different input patterns), it is clear from the anatomy that a second function, the mixing of lateral and medial inputs, must also be important. If the ideas proposed here are correct, dentate and CA3 cells should display a unique code that is a mixture of sensory cues and action.

Importantly, the mixing of cortical inputs to CA1 is already quite different; the region close to CA3 gets exclusive input from the medial entorhinal cortex whereas the region closer to the subiculum gets exclusive input from the lateral entorhinal input (Fig. 1). The same segregation holds for the CA1 projections back to cortex. This pattern of segregation is different from dentate/CA3, where all cells receive both lateral and medial information, thus presumably mixing them into a joint representation. CA1 does not appear to be part of this coding system; it is thus likely to have a role in converting the dentate/CA3 code back into the separate codes of the lateral and medial entorhinal cortex (Lisman, 1999).

Concluding remarks and predictions of the model

My goal in this discussion has been to examine the ideas incorporated into the model of Fig. 2 and to assess whether they can be usefully mapped onto the architecture of the hippocampus (Fig. 1). My general conclusion is that the correspondence is promising. The basic building blocks utilized in the model have a reasonable correspondence to the capabilities of the cortex and hippocampus. The more specific question, whether any of the functional dualities inspired by the model (C/A, non-self/self) underlie the structural duality of entorhinal inputs, cannot yet be answered with any certainty. The idea that the medial entorhinal encodes aspects of self whereas the lateral entorhinal encodes the outside world (non-self) leads to experimentally testable predictions, as outlined in the following paragraphs.

Representation of self-action on the T-maze in the medial entorhinal cortex

It should be possible to test the hypothesis proposed here by recording from the entorhinal cortex during the T- and plus-maze paradigms that demonstrate motor/action information in the hippocampus. The specific prediction is that the medial, but not the lateral entorhinal cortex should encode motor/goal information. Preliminary evidence indicates that this prediction is correct (Lipton et al., 2006).

Unique conjunctions of non-self/self in the dentate/CA3; cue information in the lateral entorhinal cortex

A second set of predictions has to do with the changes in representation. The dentate and CA3 should have cells that represent conjunction of non-self and self (e.g. cue and action) and this conjunction should not be present in layers 2 and 3 of the entorhinal cortex. An example of such a conjunction would be a cell that responded to scene, but only in conjunction with a cued action (Wirth et al., 2003). In these experiments, the scene and cue information should be encoded in the lateral entorhinal; the action taken (which may or may not be consistent with the cue) should be encoded in the medial entorhinal.

Conditioned fearful stimuli vs. the emotion of fear

The output of the basolateral amygdala represents a sensory signal, the conditioned stimulus (CS), and may well be source of the hippocampal response to the CS that develops after conditioning (Berger et al., 1976). Because these signals are non-self similar signals would be predicted in the lateral entorhinal cortex. In contrast the further processing in the amygdala that occurs in the central nucleus (Pare et al., 2004; Balleine and Killcross, 2006) is thought to represent the emotion of fear and to evoke fear-related responses in the hypothalamus and brainstem. Such emotional responses are a property of self and would be predicted to occur in the medial entorhinal cortex.

Connectivity with areas mediating personal/extra-personal attention

If there is a fundamental segregation of information about self and non-self in the entorhinal cortex, might one expect to find functionally related subdivisions at earlier stages of cortical processing? In this regard it is interesting that very recent work (Committeri et al., 2007; Ortigue et al., 2006) points to two very different forms of hemi-neglect due to brain injuries. One form, termed “extra-personal”, leads to neglect of one half of the external world; the other form, termed “personal” leads to neglect of half of the body. These forms can be doubly dissociated and involve injuries to different brain regions. It will be of interest to determine whether these regions have selective connections to the medial and lateral entorhinal cortex.

Note added in proof

I have recently become aware of other works on cortical and subcortical processing that posits a separate neural system for self-referential processing (Buckner and Carroll, 2007; Northoff et al., 2006).

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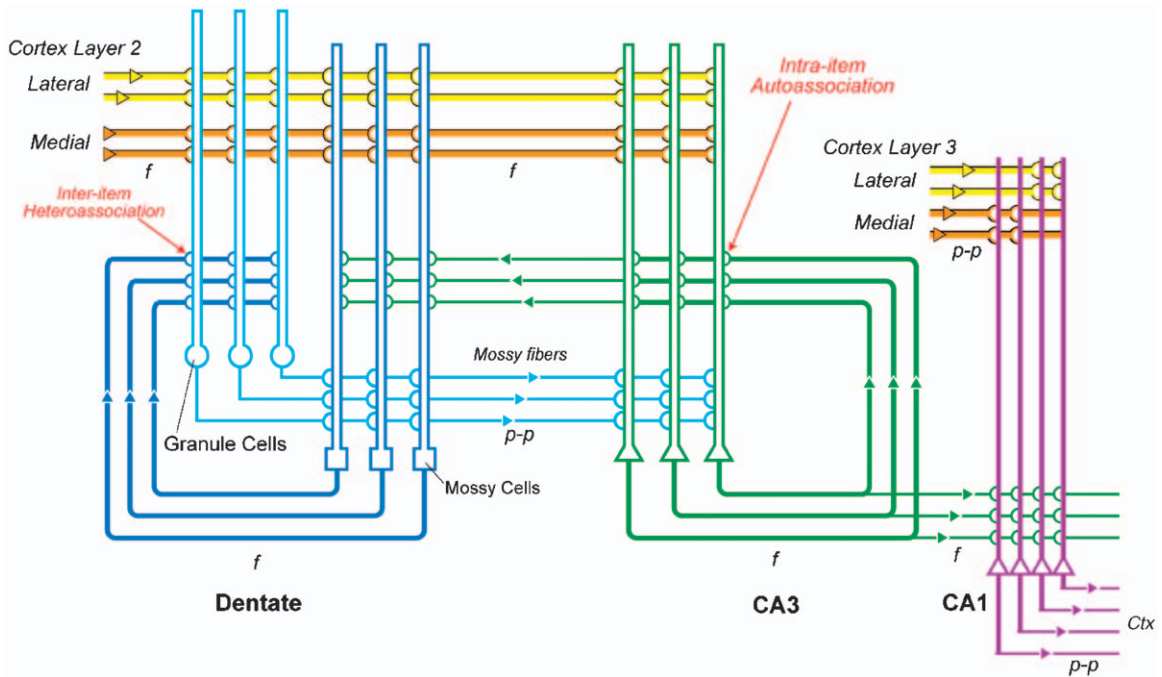


Plate 33.1. Wiring diagram of the hippocampus (interneurons excluded) showing dual inputs from the lateral and medial entorhinal cortex. The layer 2 cortical inputs to the dentate and CA3 diverge fan out (f) widely over these networks and then provide convergent input to individual dentate granule cells. In contrast, the layer 3 cortical inputs are specialized for individual subregions of CA1. This is an example of a point-to-point (p-p) connection. Within the hippocampus, granule cells provide input, via mossy fibers to the mossy cells of the dentate and to CA3 cells. CA3 cells make feedback connections to themselves and to the mossy cells of the dentate. These, in turn, provide excitatory input to granule cells in the inner third of the granule cell dendritic tree. (For B/W version, see page 616 in the volume.)

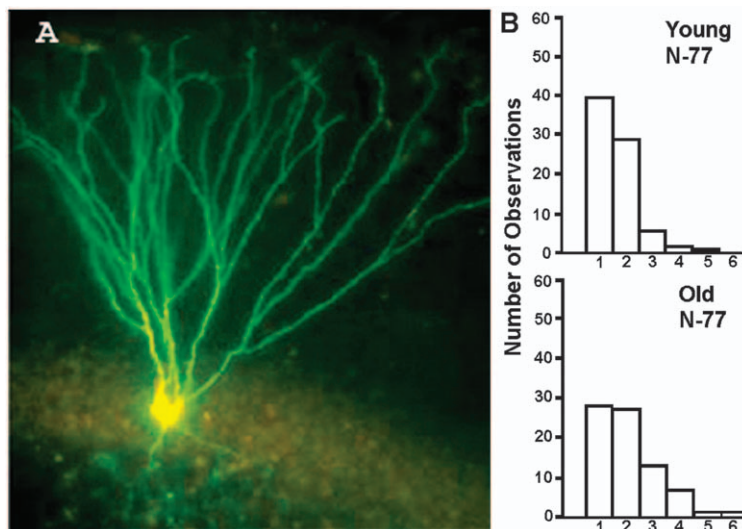


Plate 36.1. (A) Two representative granule cells filled with 5,6 carboxyfluorescein from the dentate gyrus of a 24-month-old rat. (B) Histograms showing the numbers of carboxyfluorescein injections that resulted in single, double, triple, or greater numbers of granule cells filled with dye. Aged rats showed significantly increased electrotonic coupling compared to young animals. This may account for the increased excitability of old granule cells. Adapted with modifications from Barnes et al. (1987). (For B/W version, see page 665 in the volume.)