Interactions between the entorhinal cortex and hipocampal formation
Kloosterman, F.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 6

General conclusions

Fabian Kloosterman
In the preceding chapters, the interactions between the hippocampal formation and the parahippocampal region, particularly the entorhinal cortex, have been studied using a combination of anatomical (chapter 2) and electrophysiological (chapters 3-5) techniques. The organization and functionality of re-entry circuits in the hippocampal-parahippocampal system was a central theme in all studies. The results that were obtained provide valuable clues about possible operations of the hippocampal memory system. In this final chapter I will summarize and discuss the main findings and conclusions of this thesis.

1 Anatomical organization and physiology of hippocampal output to the entorhinal cortex (chapters 2 & 3)

One characteristic of the connections within the PHR and HPF as well as input projections from the PHR to the HPF is their topographical organization. With respect to the connections from the PHR to the HPF this organization is clearly present along both the septo-temporal and transverse axes (Amaral et al., 1991, Burwell and Amaral, 1998, Dolorfo and Amaral, 1998a, Naber et al., 1999, Naber et al., 2001, Steward, 1976, van Groen and Wyss, 1990, Witter, 1993). In chapter 2, it was shown that the return projections from the subiculum to the ento-, peri- and postrhinal cortices also display a clear topographical pattern, which matches remarkably well the organization of input projections that the subiculum receives from the PHR. In the introductory chapter 1, it was argued that the organization of input projections in the hippocampal memory system might have the functional consequence that distinct sensory information flows are kept segregated. The results described in chapter 2 imply that this segregation is maintained on the output side. We may thus propose that the hippocampal memory system is organized by way of multiple parallel circuits (fig. 6.1, see also Naber et al., 2000).

Subicular projections to the entorhinal cortex (and in fact also to the peri- and postrhinal cortices) terminate predominantly in the deep layers (V and VI), and only sparsely in superficial layers (I-III) as was demonstrated in chapter 2 (see also Köhler, 1985). Thus the population of neurons that receives hippocampally-processed information (layer V) to a major extent does not overlap with the population of neurons that give rise to the projection to the hippocampal formation (layers II and III). In chapter 3, we indeed showed that electrical stimulation of subiculum evoked a simultaneous discharge of layer V pyramidal neurons, which was evident as a sharp spike potential/current sink in layer V at the population level. Two properties of the subicular-evoked response in entorhinal deep layers should be mentioned here. First, the layer V population spike is subject to facilitation, but not depression, if two stimuli are presented in short succession (i.e. 10-500 ms interval). This contrasts with pathways in the hippocampal formation and with entorhinal input pathways to the hippocampal formation, which generally show paired-pulse depression at short intervals, due to local feedback inhibitory circuitry. Thus, as was suggested in chapter 3, feedback inhibition may not be prominent in the subiculo-entorhinal pathway (see also Finch et al.,
The second feature of the entorhinal deep layer response is that the population spike appears to propagate into superficial layers along the apical dendrite of layer V pyramidal neurons. Such a back-propagation of action potentials into dendrites has been implicated in the induction of synaptic plasticity. Changes of synaptic strength occur only if the dendritic action potential is coincident with synaptic input within a certain time window (Markram et al., 1997). Furthermore it was demonstrated in hippocampal (Nakamura et al., 1999) and neocortical (Larkum et al., 2003) pyramidal neurons that repetitive stimulation can cause back-propagating action potentials that are capable to generate calcium waves along the dendrites, which can trigger intracellular cascades for the induction of synaptic plasticity. What inputs to the apical dendrites of layer V neurons may be subject to this plasticity? Certainly any input terminating in superficial layers has the potential of making contacts with these dendrites, but up to now such a connection has only be firmly established for presubiculat inputs (van Haeften et al., 2000). Assuming that other cortical areas project to layer V apical dendrites as well, how could these inputs be temporally and meaningfully coordinated with the subiculum evoked back-propagating action potential such that intracellular processes leading to plasticity are triggered? What follows is a very speculative account. Suppose sensory information reaches the superficial layers of the entorhinal cortex via peri- and postrhinal cortices and evokes an excitatory response in layer II and III neurons, some of which may discharge. Layer V apical dendrites may also receive excitatory input, but are (initially) much less prone to firing in response to this input (e.g. since synapses are located far from the action potential trigger zone in the axon-hillock). Several subicular and CA1 neurons may receive direct input from layer III neurons or indirect input from layer II neurons (via dentate gyrus and CA3). The combined result would be that by virtue of the topographical organization of the connections a limited number of neurons in CA1 and subiculum will fire and return activity to the same patch of entorhinal cortex where activity initially originated (i.e. chapter 2). Subsequently, some of the recipient entorhinal layer V neurons may discharge and produce a back-propagating action potential in their apical dendrite. If the same neurons also received input from cortical inputs at the very beginning, these synapses may undergo facilitation. The end result is that layer V neurons would now fire in response to the initial cortical input, bypassing the necessity of hippocampal input.

As illustrated in figure 6.1 and also mentioned in chapter 1, area CA1 also projects to the entorhinal cortex (Tamamaki and Nojyo, 1995, van Groen and Wyss, 1990). There are strong indications that the topographical and laminar organization of this projection is similar to that of the subiculo-entorhinal pathway. Moreover, both CA1 and subiculum are in the position to receive similar information from the entorhinal cortex, directly from layer III (Steward and Scoville, 1976, Witter, 1993), or indirectly via layer II and dentate gyrus/CA3. This of course raises the question whether CA1 and subiculum are functionally equivalent or distinct. Several observations suggest that the latter is the case. For example it appears that efferent projections of subiculum are much more widespread than those of area CA1.
Moreover, single CA1 neurons may project to a variety of targets, whereas subiculum neurons preferentially have a single target (see discussion chapter 2). There are physiological differences between CA1 and subiculum as well. Most noticeably, in subiculum there is a relatively large population of bursting neurons, but these are not present in area CA1. Large differences are also found with respect to the firing behavior of single CA1 and subiculum neurons during behavioral tasks. CA1 pyramidal neurons fire in relation to the actual position of the animal in the environment, i.e. they have ‘place fields’ (O'Keefe, 1979). If the animal is transferred from one environment to another, new place fields develop. Subicular cells do have location-related firing, but this is much less specific and they tend to generalize among environments (Sharp, 1999). This means that a subicular neuron that discharges when the animal is in a particular location in the arena, it will discharge in a similar location in another arena. Firing patterns of subicular and CA1 neurons also differ during a delayed non-match to sample (DNMS) task (Hampson et al., 2000). CA1 neurons captured some task-relevant events (i.e. place and phase of the task), but they did not exhibit much activity during the delay phase of the task, i.e. they did not hold information for longer times. Subicular neurons, however, did exhibit delay-dependent activity, although they coded much less for task-relevant events. Remarkably, this behavior of subicular cells (i.e. the less specific location-related firing and generalization among environments, as well as the activity during a DNMS task) is similar to that of entorhinal neurons (Frank et al., 2000. Hampson et al., 2000. Quirk et al., 1992. Sharp, 1999. Suzuki et al., 1997. Young et al., 1997).

These data suggest that CA1 and subiculum exert different functions. A prominent pathway, however, exists from CA1 to subiculum (Amaral et al., 1991), so that the two structures strongly interact. It would be interesting to see what kind of interaction this is and whether it is dependent on behavior or modulatory input from serotonin, dopamine or acetylcholine neurotransmitter systems.

2 Inter-laminar connections in the entorhinal cortex: interplay between the output and input streams (chapters 3 & 4)

In addition to the relay of information from the neocortex to the hippocampal formation and back to the neocortex, the entorhinal cortex may mediate interaction between the input and output streams by way of the connections between deep and superficial layers. In chapter 3, we demonstrated that stimulation of hippocampal output could indeed result in a response in the superficial layers, which followed the population spike in deep layers. Moreover, blocking the deep layer responses by local application of a glutamate receptor antagonist also abolished superficial layer responses, showing that this was indeed the result of inter-laminar connections.

The deep-to-superficial layer connections were described already in the early 20th century by Ramón y Cajal (see pages 689-698 in Ramón y Cajal, 1955) and recent anatomical
Figure 6.1 Two re-entrant loops in the hippocampal-entorhinal system. A short loop is defined by the connections between EC-III, CA1/subiculum and EC-V. A long loop is defined by the connections between EC-II, DG/CA3, CA1/subiculum and EC-V. Multiple parallel loops may be present as a consequence of segregation due to the topographical organization of the input and output projections.

studies confirmed these projections (Dolorfo and Amaral, 1998b, Köhler, 1986, 1988, van Haeften et al., 2003). In a very recent study, it was demonstrated that these projections formed mainly excitatory contacts with both principal and interneurons in superficial layers (van Haeften et al., 2003).

After repetitive stimulation of subiculum, delayed current sinks were found in CA1-slm and in DG-ml (chapter 4). This indicated that among the superficial layer neurons that were recipients of deep layer inputs were those that also provided the input to the dentate gyrus and area CA1 (see also Bartesaghi and Gessi, 2003, Deadwyler et al., 1975, Wu et al., 1998). Apparently, hippocampal output may re-enter hippocampal sub-fields via deep entorhinal layers (see fig. 6.1). What could be the functional relevance of inter-laminar communication in the entorhinal cortex and subsequent re-entrance to the hippocampal formation? As depicted in figure 6.1, the re-entrance pathways through layer II and III can be considered as part of a long and a short entorhinal-hippocampal-entorhinal loop, respectively. The topographical organization of the connections in the entorhinal-hippocampal system (see chapters 1 & 2) assures that these loops are functionally closed. Activity within such loops may circulate or reverberate and as such these circuits could act as dynamic information stores (Hebb, 1949). As already alluded to above, persistent activity was found in the entorhinal cortex and subiculum during the delay phase of a delayed non-match to sample.
task (Hampson et al., 2000, Suzuki et al., 1997, Young et al., 1997). According to Eichenbaum and Cohen (2001), the sustained activity of neurons in the entorhinal cortex and other areas of the parahippocampal region indicate that these regions are buffering information that than can be used and manipulated by other structures (e.g., the hippocampal formation). We may speculate that re-entrant circuits, e.g., the entorhinal-subiculum-entorhinal loop, maintain the persistent activity. It should be noted that as CA1 does not show delay-dependent activity in the DNMS task (Hampson et al., 2000), the loops involving this area might not be involved in the generation of persistent activity. Also, other mechanisms may, either alone or in combination with re-entrant circuits, support persistent activity (i.e., see Egorov et al., 2002). Up to date, however, there is no direct evidence that reverberation really takes place in behaving animals.

Another view on the function of the connections between hippocampal output and input via intra-entorhinal connections is that these connections could support the comparison of hippocampally-processed information with new or buffered information in the entorhinal cortex. In this way the circuit may act as a ‘novelty detector’ (Naber et al., 2000), signaling when a previously unknown stimulus arrives. In the model of Lorincz et al. (2000, 2002), the hippocampal-entorhinal system is regarded as a ‘novelty-detecting reconstruction network’, which develops representations of series of events and is able to make predictions about ongoing events based on these stored representations. In their model, the connection from entorhinal layer V to layer II serves to compare the predicted output of the hippocampal formation (arriving in layer V) and the actual neocortical input. Any deviation between the two inputs, they assume, leads to changes in the network to minimize this error.

A novel and interesting finding that we reported in chapter 4 is that the two re-entrance pathways (i.e., via layer II and III respectively) differed markedly in their sensitivity to anesthetic agents. Under urethane anesthesia both re-entrance pathways could be activated (chapter 4), but under ketamine/xylazine (chapter 4) or sodium thiopental (Bartesaghi and Gessi, 2003) only the re-entrance pathway to CA1-slm could be activated. It is difficult to see what single mechanism could explain these results. Synaptic responses of layer II stellate neurons are controlled by both fast and slow GABAergic inhibitory potentials, which are usually powerful enough to prevent the cells from discharging (Finch et al., 1988, Jones, 1993, 1994). This inhibition could explain the absence of re-entry via layer II to the dentate gyrus under sodium thiopental anesthesia, since this anesthetic is a barbiturate that enhances GABAergic receptor function. Layer II basket cells are one type of interneuron that could exert an inhibitory influence on layer II stellate neurons (Jones and Buhl, 1993, Wouterlood et al., 1995). These basket cells, however, receive a strong excitatory NMDA-receptor dependent input (Jones and Buhl, 1993) and thus one would expect that under ketamine/xylazine anesthesia, via the antagonistic properties of ketamine on NMDA-receptors, these interneurons would become less active what would result in disinhibition of layer II cells, facilitating re-entrance into the dentate gyrus through layer II. In our
General conclusions

experiments, however, we did not find support for this mechanism, since under ketamine/xyazine anesthesia the re-entrance from layer II to the dentate gyrus is blocked. Therefore we may hypothesize that a strong NMDA-receptor component affects preferentially the transmission of information from deep layers to layer II, but not layer III, which may explain the difference between the two re-entrance pathways under ketamine/xyazine anesthesia.

The finding that re-entrance pathways trough layer III and II are differentially influenced by various anesthetic agents, may indicate that also under more physiological circumstances activity in these pathways can be modulated separately. Several possible mechanisms for such modulation can be suggested. For example, it would be interesting to see whether these pathways are modulated by behavior (e.g. slow-wave sleep, REM sleep, waking), as was demonstrated for several pathways of the hippocampal formation (Winson and Abzug, 1978). Such a behavioral modulation of synaptic transmission could also be mediated by sub-cortical inputs to the entorhinal cortex, which contain a variety of neuromodulatory substances (serotonin: Vertes et al., 1999; dopamine: Köhler et al., 1991; acetylcholine: Alonso and Kohler, 1984; noradrenaline: Loughlin et al., 1982, Swanson et al., 1987) and which show a different amount of activation during specific periods of the sleep-wake cycle (see Pace-Schott and Hobson, 2002). Ample evidence exists that these neurotransmitter systems may affect both the intrinsic membrane properties and synaptic inputs of entorhinal neurons (serotonin: Grunschlag et al., 1997, Schmitz et al., 1998a, Schmitz et al., 1998b, c, 1999; dopamine: Pralong and Jones, 1993, Stenkamp et al., 1998; acetylcholine: Chapman and Racine, 1997, Cheong et al., 2001, Dickson and Alonso, 1997, Dickson et al., 2000, Fantie and Goddard, 1982, Mizumori et al., 1992, Richter et al., 1999, Robinson and Racine, 1986; noradrenaline: Assaf et al., 1979, Pralong and Magistretti, 1994, 1995). It is not yet clear, however, whether deep-to-superficial layer inputs are affected differentially by these neurotransmitters. At a smaller time scale, we may speculate that the rhythmic variation of membrane potential during waking and REM sleep (i.e. theta oscillations, 4-12 Hz, Alonso and Garcia-Austt, 1987a) or during SWS (i.e. slow oscillations, chapter 5) could influence the strength of deep-to-superficial projections. In this scenario, only inputs arriving in deep entorhinal layers during a specific phase of these oscillations may be transmitted to superficial layer neurons. In addition to the above-proposed mechanism, another possible way to differentially recruit inter-laminar projections is by way of the frequency of inputs. Layer III neurons can be activated by low frequency inputs, but are strongly inhibited by high frequency inputs. In contrast, layer II neurons are silent during low frequency inputs and only start to fire at high frequency inputs (Gloveli et al., 1997, Jones, 1995).
Spontaneous activity patterns reflecting hippocampal-entorhinal communication (chapter 5) and the possible operation of the hippocampal memory system

As pointed out in chapters 1 and 5, interactions between the hippocampal formation and entorhinal cortex may lead to the transient formation of cell ensembles, and these may be studied by recording the action potentials of many neurons simultaneously (Deadwyler and Hampson, 1997, Hampson et al., 2001, Kralik et al., 2001). However, spontaneously occurring extra-cellular potential changes at the population level (i.e. oscillations and other mass potentials) may also reveal how the activity within and between brain structures is organized and coordinated. In the hippocampal-entorhinal system several activity patterns have been identified, each characterized by their own site and mechanism of generation, by their relation to behavioral state (i.e. exploration, immobility, REM-sleep, SWS-sleep) and by their interactions with other activity patterns. Different functional roles during memory processes have been proposed for most of these activity patterns.

In chapter 5, we investigated slow oscillations in the entorhinal-hippocampal system and their relation to other activity patterns. Slow oscillations are a characteristic feature of the neocortical electroencephalogram in slow-wave sleep (Steriade et al., 1993a, b, Steriade, 2000), but few studies have looked at these oscillations in the hippocampal-entorhinal system (Collins et al., 1999). We demonstrated that entorhinal and hippocampal slow oscillations were locally generated. Sources were present in EC-II/I and neurons in all entorhinal layers were found that fired in relation to the slow oscillations. In the hippocampal formation, slow oscillations sources were located in CA1-slm and DG-gc, and these were coherent with the entorhinal sources. Distinct relations were also found between the slow oscillations and entorhinal sharp potentials and gamma activity. Sharp potentials were associated with current sinks in deep and superficial entorhinal layers, possibly reflecting inter-laminar communication (see chapter 5). What could be the functional role of coordinated slow oscillations and their relations to other patterns in the operation of entorhinal-hippocampal networks in memory processes? Before attempting to answer this question, I will first briefly review one prevalent view of hippocampal operation.

The two-stage model of memory trace formation (Buzsaki, 1989, 1996) states that memory traces are initially stored in the hippocampal network during active waking behavior. During subsequent slow-wave sleep, the stored representations are spontaneously re-expressed in the hippocampal network and transmitted to cortical structures to facilitate long-term consolidation of the memory traces. Support for this theory is provided by electrophysiological studies. First, the specific distribution of hippocampal-entorhinal activity patterns appears to indicate that information flow is hippocampal-petal during active waking and hippocampal-fugal during slow-wave sleep (see theta/gamma oscillations in fig. 6.2A and sharp waves/ripples in fig. 6.2B) (Buzsaki, 1996, Chrobak et al., 2000).

During active waking, theta oscillations (4-12 Hz) are present in the entorhinal cortex and hippocampal formation (Buzsaki et al., 1986, Buzsaki, 2002, Buzsaki et al., 2003.
General conclusions

Chrobak and Buzsaki, 1998, Frank et al., 2001, Jeffery et al., 1995, Leung, 1998, Mitchell and Ranck, 1980), which are dependent on cholinergic and/or GABAergic inputs from the medial septum (Asaka et al., 2002, Bland and Bland, 1986, Dickson et al., 1994, Jeffery et al., 1995, Lee et al., 1994, Leung et al., 1994, Mitchell et al., 1982). Theta oscillation current sources in the entorhinal cortex are localized in superficial layers and particularly neurons in layers II and III discharge in relation to the theta oscillations (Alonso and Garcia-Austt, 1987a, b, Chrobak and Buzsaki, 1998, Dickson et al., 1995, Stewart et al., 1992). In the hippocampal formation, theta oscillations current sources are found in CA1-slm and in the dentate gyrus (Brankack et al., 1993, Buzsaki et al., 1986), which both receive input from the entorhinal superficial layers (Dolorfo and Amaral, 1998a, Steward and Scoville, 1976). Associated with the theta oscillations are fast gamma oscillations and related neuronal firing in entorhinal cortex layer II (Chrobak and Buzsaki, 1998, Csicsvari et al., 2003, Leung, 1998), which drive gamma oscillations in the dentate gyrus (Bragin et al., 1995) (fig. 6.2A). Theta oscillations are also found in CA1-rad and CA1-pyr, presumable due to patterned inhibitory input from local interneurons or the medial septum and excitatory inputs from CA3 (Buzsaki, 2002) (fig. 6.2A). In addition, gamma oscillations are present in CA1 and these may at least in part originate in CA3 (fig. 6.2A) (Csicsvari et al., 2003).

During slow-wave sleep and awake immobility, the hippocampal system switches to a different mode of operation. Theta oscillations are not present and gamma oscillations are attenuated. Instead, synchronous bursts, i.e. sharp waves and high frequency ripple activity, are found in CA1 (Buzsaki, 1986, Buzsaki et al., 2003, Suzuki and Smith, 1987), presumably originating in CA3 (Csicsvari et al., 2000) (fig. 6.2B). These sharp waves are transmitted to the entorhinal deep layers, but not to the superficial layers (Chrobak and Buzsaki, 1994) (fig. 6.2B). The alteration from cortico-hippocampal to hippocampal-cortical communications has been proposed to be mediated by the level of acetylcholine provided by septal inputs, since synaptic transmission along several pathways in the hippocampal formation are differentially influenced by acetylcholine (Hasselmo, 1999).

The presence of entorhinal cortex mediated theta/gamma oscillations in the HPF during waking and CA1 sharp waves during SWS, has been taken as evidence supporting Buzsaki’s two-stage model. Another line of evidence that supports the two-stage model is the finding that experience-specific neuronal ensemble activity is reactivated during subsequent slow-wave sleep (Kudrimoti et al., 1999, Nadasdy et al., 1999, Shen et al., 1998, Wilson and McNaughton, 1994). Reactivation may also occur in neocortical areas in coordination with the hippocampal formation (Hoffman and McNaughton, 2002, Sutherland and McNaughton, 2000). Whether and how the re-expressed neuronal ensemble activity is involved in the actual memory consolidation process is however not yet clear. In summary, Buzsaki’s two-stage model states that sensory information is relayed to the hippocampal formation via the entorhinal cortex. The new experiences are recorded in the hippocampal networks. During slow-wave sleep, the hippocampal formation switches to playback mode and stored memory
A. waking

**Theta Oscillations**

- EC → DG → CA3 → CA1
- MS

**Gamma Oscillations**

- EC → DG → CA3 → CA1

B. Slow-wave sleep & ketamine/xylazine anesthesia

**Sharp Waves/Ripples**

- EC → DG → CA3 → CA1
- amygdala (amyg) → ctx

**Slow Oscillations**

- EC → DG → CA3 → CA1

**Sharp Potentials**

- EC → DG → CA3 → CA1
- amygdala (amyg) → ctx

**Gamma Oscillations**

- EC → DG → CA3 → CA1

**Figure 6.2** Overview of the areas in the hippocampal formation and the entorhinal cortex that are engaged in spontaneous activity patterns during waking (A) and slow-wave sleep (B). For each activity pattern (i.e., theta oscillations, gamma oscillations, slow oscillations, sharp potentials, and sharp waves/ripples), a separate scheme is presented. Orange colors indicate activities present in the entorhinal cortex and/or those that may be transmitted from the entorhinal cortex to the hippocampal formation. Blue colors indicate activities generated in the hippocampal formation and which may be transmitted to the entorhinal cortex. Darker colors represent more robust activation. Arrows indicate the possible pathways involved in the communication between the entorhinal cortex and hippocampal formation during the spontaneous activity patterns. Dashed arrows, which are marked by a question mark, indicate pathways that are possibly involved in the hippocampal-entorhinal communication during the activity patterns, but no conclusive data exist as yet. The generation of theta oscillations in the hippocampal formation and entorhinal cortex critically depends on inputs from the medial septum (MS), as indicated in A.
traces are played back, presumably during sharp waves, and ‘broadcast’ to the neocortex for long-term storage (i.e. consolidation).

Returning to the question posed above: how do the slow oscillations, sharp potentials and gamma activity that are present in the anesthetized state (chapter 5), assuming that they are akin to those encountered during natural sleep, fit in this emergent picture of hippocampal operation? We noted in chapter 5 that slow oscillations are coherent between the entorhinal cortex and the hippocampal formation. It is possible that the hippocampal slow oscillations are mediated by the entorhinal-hippocampal projections. However, slow oscillations in CA1-slm showed a phase-lead relative to entorhinal slow oscillations, which would suggest that the slow oscillations would flow from CA1 to EC. A phase-relation of an oscillation with a narrow spectral peak such as the slow oscillation, however, cannot be simply translated into a time-delay, since phase shifts depend on several components in addition to transmission delays (Boeijinga and Lopes da Silva, 1989). Thus, our data do show that slow oscillations are coherently present in the hippocampal formation and entorhinal cortex, but at the moment it is still unclear how exactly the slow oscillations flow between these structures.

Concerning the entorhinal sharp potential, the available data (chapter 5, Paré et al., 1995) allows us to conclude that the direction of information flow during sharp potentials is from the entorhinal cortex to the hippocampal formation, unlike the sharp wave/ripple events (fig. 6.2B). It is also possible that the deep-to-superficial projection in the entorhinal cortex contribute to the generation of sharp potentials (chapter 5).

Even though gamma oscillations appear to be attenuated during slow-wave sleep, as mentioned above, they are not completely abolished. In chapter 5 we reported that gamma oscillations were present in entorhinal layer II and the dentate gyrus under ketamine/xyloxazine anesthesia and are likely transmitted from the entorhinal cortex to the dentate gyrus. Unlike in the behaving rat, however, gamma oscillations were not found in area CA1.

In summary, it appears that information flow during states characterized by slow oscillations is not limited to the direction of hippocampal formation to (entorhinal) cortex. In addition, during theta oscillation states, information flow may also be opposite to what the model states, since a proportion of entorhinal deep layer neurons do fire in relation to the theta oscillation (Alonso and Garcia-Austt, 1987b, Dickson et al., 1995, Frank et al., 2001), possibly mediated by inputs from CA1 and subiculum. Does this mean that the model is not valid? Not necessarily. It is unlikely that the hippocampal formation is just replaying previously stored memory traces, regardless of what is happening in other cortical areas. Rather coordination of activities will presumably be required for successful consolidation of memory traces. Thus it may be proposed that the slow oscillation, sharp potentials and gamma oscillations provide the mechanisms to coordinate the hippocampal and cortical activities at short and long time scales during memory processes.