

The rhinal cortices: a wall of inhibition between the neocortex and the hippocampus

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Abstract

Anatomical data indicate that the parahippocampal region, comprised of the perirhinal (PRC), postrhinal (POR) and entorhinal (ERC) cortices, is an essential link between neocortex and hippocampus. Lesion studies demonstrated that memory functions previously ascribed to the hippocampus depend on the integrity of the rhinal cortices. This review will consider recent data suggesting that the ERC and PRC, far from being passive relay stations, actively gate impulse traffic between neocortex and hippocampus, because they are endowed with a powerful intrinsic inhibitory system. It is proposed that the cross-talk between PRC and ERC is not organized to unrestrictedly transfer information, but to select relevant inputs. The implication of these new evidences for the propagation of epileptiform activity will be considered.

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Contents

1. Extrinsic and intrinsic connections of rhinal cortices	102
2. Physiology of perirhinal–entorhinal interactions.	102
3. Intrinsic inhibitory mechanisms that control propagation across rhinal cortices	104
4. Associative longitudinal propagation of excitation within PRC and ERC	106
5. Implication for the genesis and propagation of epileptiform activity.	107
6. Conclusions.	107
Acknowledgements.	108
References.	108

Abbreviations: ERC, entorhinal cortex; PRC, perirhinal cortex; POR, postrhinal cortex; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; RS, rhinal sulcus

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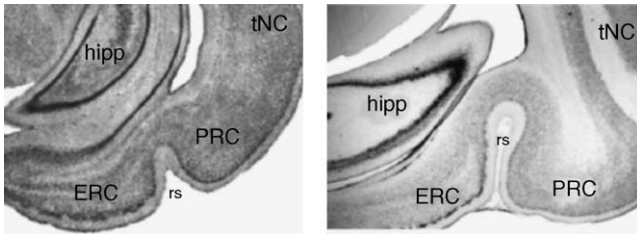


Fig. 1. Coronal sections of the parahippocampal region of the guinea pig (left) and the cat (right). PRC, perirhinal cortex; ERC, entorhinal cortex; rs, rhinal sulcus; hipp, hippocampus; tNC, temporal neocortex.

The parahippocampal cortex is the gateway to the hippocampus. It is critically involved in complex functions, such as memory, object recognition, sensory representation and spatial orientation (Witter and Wouterlood, 2002; Murray and Richmond, 2001; Suzuki and Eichenbaum, 2000). Moreover, it is primarily and selectively damaged during early stages of neurological and psychiatric diseases, such as temporal lobe epilepsy, dementia and schizophrenia (Bernasconi et al., 2003; Witter and Wouterlood, 2002; Gomez-Isla et al., 1996; Du et al., 1995; Van Hoesen et al., 1991; Arnold et al., 1991). Various parcellations of the parahippocampal region have been proposed (Witter and Wouterlood, 2002). In this review (Fig. 1), we will use a restricted definition that includes the perirhinal (PRC) and entorhinal (ERC) cortices, located lateral and medial to the rhinal fissure respectively, as well as the caudally located postrhinal cortex (POR). In primates, the latter region is also referred to as parahippocampal cortex, or area TH and TF (Burwell, 2001; Witter et al., 2000; Dolorfo and Amaral, 1998; Burwell et al., 1995). On the basis of cytoarchitectural, immunohistochemical and hodological criteria, the PRC is further sub-divided in two parallel cortical bands, areas 35 (medially) and 36 (laterally). Similarly, the ERC has been divided in two major sub-fields, the rostral-lateral ERC and the caudal-medial ERC (Uva et al., 2004; Dolorfo and Amaral, 1998).

1. Extrinsic and intrinsic connections of rhinal cortices

The defining feature of the parahippocampal region resides in its reciprocal connections with uni- and polymodal association neocortical areas and with the hippocampal formation. Even though strict reciprocity between medial temporal lobe and the neocortex has been questioned in primates (Lavenex et al., 2002) and is not unequivocal in other species, tract tracing studies indicate that information transfer from the neocortex to the hippocampus depends on impulse propagation through a sequence of longitudinal bands of cortex parallel to the rhinal fissure (neocortex to area 36, to area 35, to ERC and back). The progression of impulse traffic into discrete steps is not absolute, however, as some deep neocortical neurons project beyond area 36 into area 35 and the ERC (Burwell and Amaral, 1998a,b; Saleem

and Tanaka, 1996; McIntyre et al., 1996; Suzuki and Amaral, 1994). As a general rule, medially directed axons (from neocortex to PRC and from PRC to ERC) mainly originate in superficial layers, whereas return projections directed to the neocortex originate in deep layers (Burwell and Amaral, 1998b; Saleem and Tanaka, 1996; Witter et al., 1986; Deacon et al., 1983; Van Hoesen and Pandya, 1975).

PRC to ERC connection fibers terminate in superficial layers of target areas (Burwell, 2000; Burwell and Amaral, 1998b; Naber et al., 1997; Burwell et al., 1995; Suzuki and Amaral, 1994; Sorensen, 1985; Deacon et al., 1983). In the rat, fibers originating from areas 36 and 35 mostly terminate in the medial and lateral ERC, respectively. ERC efferent fibers target all cortical layers of area 35 and a small contingent extends to area 36 and to the temporal neocortex (Burwell and Amaral, 1998b; Suzuki and Amaral, 1994; Swanson and Kohler, 1986; Sorensen, 1985; Deacon et al., 1983; Kosel et al., 1982). Anatomical studies also demonstrated that POR neurons are reciprocally connected with cells in all layers of the caudal-medial and lateral parts of the ERC (Burwell and Amaral, 1998b). In addition, well-developed systems of associative fibers that run parallel to the rhinal fissure connect subregions of both PRC and ERC and reciprocally link PRC to POR (Burwell and Amaral, 1998a; Dolorfo and Amaral, 1998). The connection pattern of rhinal cortices to the hippocampus proper has been extensively reviewed (Burwell and Witter, 2002; Lopes da Silva et al., 1990) and will not be discussed here.

2. Physiology of perirhinal–entorhinal interactions

Although little physiological work has been performed on the rhinal cortices, it is typically assumed that they faithfully transmit inputs from the neocortex to the hippocampus and vice versa. In fact, many theories of episodic memory consolidation rely on the existence of a fast transfer of information via highly synchronized discharges of large numbers of neurons in parahippocampal cortices (Pennartz et al., 2002; Buzsáki, 1989). For instance, one model posits that during waking, information of neocortical origin is initially stored in the hippocampus via changes in the strength of connections between pyramidal neurons. During sleep, synchronized discharges of CA3 neurons “replay” representations stored in CA3 and, via synchronous activation of the rhinal cortices, reactivate neocortical neurons representing features of the event of interest. Ultimately, this replay would lead to long-term synaptic changes that reinforce selective connections within associative cortical networks (Pennartz et al., 2002; Buzsáki, 1989). Although, evidence of replay was obtained in the hippocampus, proof that these signals reach the neocortex is lacking. At present, this hypothesis is based on evidence that neocortical (somatosensory) and hippocampal activity during sleep spindles and delta waves are highly correlated (Sirota et al., 2003; Siapas and Wilson, 2001). However, as

we will see in the next section, the rhinal cortices do more than merely relay synchronous activity between neocortex and hippocampus. Rather, they support a gating mechanism whose properties remain to be identified.

In spite of the demonstration of well-defined reciprocal connections between temporal neocortex and rhinal cortices, extracellular recordings and optical imaging studies have revealed that PRC–ERC and ERC–PRC interactions do not involve massive neuronal activation. Rather, there is a low probability that PRC neurons will transfer neocortical inputs to ERC and reciprocally. For instance, laminar analysis of extracellular field potentials performed in the isolated guinea pig brain preparation showed that the activity induced by stimulation of either the PRC (both areas 36 and 35) or the POR does not induce population responses in the ERC (Gnatkovsky et al., 2004; Biella et al., 2002a). Similarly, stimulation of the temporal neocortex in vivo and in the isolated guinea pig brain induced local field responses in the PRC, but did not evoke clear local responses in the ERC (Pelletier et al., 2004; Biella et al., 2002a; Naber et al., 2000). Moreover, current-source density analysis of laminar profiles demonstrated that no field responses were evoked in the PRC when the ERC is massively activated either by olfactory tract stimulation or by the hippocampal output (Biella et al., 2003).

The failure to detect propagation of neuronal activity across the rhinal fissure with laminar field potential analysis could be due to technical limitations, since this method does not reveal evoked activity unless it is laminarily segregated. However, two additional lines of evidence suggest that propagation of activity between PRC and ERC and vice versa does not involve highly synchronous neuronal discharges. First, imaging studies of intrinsic (Federico et al., 1994) and voltage-sensitive signals (Biella et al., 2003; de Curtis et al., 1999) in rhinal cortices yielded results identical to those obtained with field potential recordings. For instance, stimulation of the lateral olfactory tract induced large optical signals in the lateral ERC, via piriform-to-ERC associative fibers, as well as in the medial ERC, via the hippocampus. However, no evidence of neuronal activity propagation could be detected lateral to the rhinal fissure (Fig. 2). Second, single unit recordings confirmed that neocortex-evoked neuronal firing in the ERC is rare and sparse. In particular, temporal neocortical stimuli excited as many as 42% of perirhinal neurons compared to only 2% of ERC cells during in vivo experiments in anesthetized cats (Pelletier et al., 2004). In contrast, stimulation of the basolateral amygdala orthodromically activates $\approx 15\%$ of cells in both the PRC and ERC (Pelletier et al., 2004). Similar findings were reported with single unit and intracellular recordings in the isolated guinea pig brain (Biella et al., 2002a), where PRC/POR stimulation activated few neurons scattered in superficial and deep layers of the ERC (Gnatkovsky et al., 2004; Biella et al., 2002a).

The above data were obtained in anesthetized animals or in preparations maintained in vitro. However, the low probability rhinal transmission documented in these studies

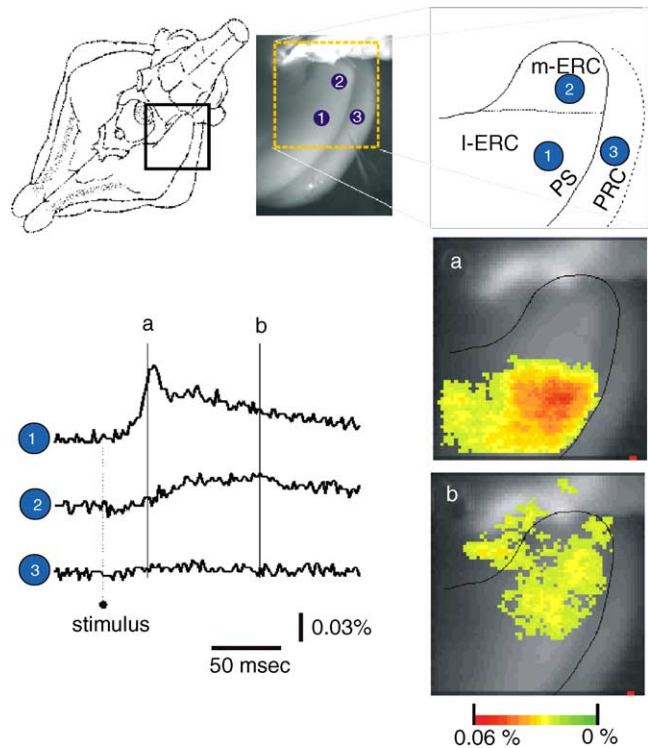


Fig. 2. Optical imaging of the propagation of neuronal activity in ERC and PRC of the isolated guinea pig brain preparation after lateral olfactory tract stimulation. Recordings were performed with a high-performance optical system (de Curtis et al., 1999; Biella et al., 2003). The isolated brain was perfused arterially with a voltage-sensitive dye (RH-795) that emits a fluorescent signal during neuronal depolarization. The optical system was centered on the square area illustrated on the drawing of the ventral view of the brain (upper left) and on the high-definition photograph (upper middle panel). The anatomical borders of the ERC and PRC are outlined in the upper right part of the figure that represents a schematic drawing of the recorded area outlined by the square dotted line (RS, rhinal sulcus). In the lower left panel, the time course of optical activity evoked by lateral olfactory tract stimulation (dotted line), recorded in the medial ERC (site 1) lateral ERC (site 2) and in the PRC (site 3) are illustrated. Optical signal was measured as fractional changes in fluorescence intensity of the response. In the lower right panels, stimulus-evoked optical changes are illustrated for the time points marked by the continuous vertical lines a and b in the left panel. Fractional fluorescence changes encoded in pseudocolors (see scale) are superimposed on brightfield image of the area defined in the upper right panel. Direct and hippocampus-mediated activities generated in the ERC are illustrated in (a) and (b). Activity does not propagate to the PRC. The border between ERC and PRC is outlined by the contour line (modified from Biella et al., 2003).

was also seen in unanesthetized behaving animals. Indeed, cross-correlation analysis of spontaneous discharges generated by simultaneously recorded temporal neocortical, perirhinal and entorhinal neurons failed to provide evidence of propagating activity in this circuit during waking and slow-wave sleep (Pelletier et al., 2004). Even synchronized neuronal discharges, such as those occurring spontaneously in relation to entorhinal sharp potentials, failed to propagate across the PRC. Similarly, population bursts accompanying large perirhinal EEG events, propagated to the temporal neocortex but not to the ERC (Pelletier et al., 2004).

In light of these findings, it is unlikely that the correlation observed *in vivo* between somatosensory neocortex and hippocampus during sleep oscillations (Sirota et al., 2003; Siapas and Wilson, 2001) depends on transfer of neocortical impulses across the rhinal cortices. More likely explanations include thalamic transfer of neocortical activity to the ERC and hippocampus (Dolleman-Van der Weel et al., 1997; Wouterlood et al., 1990) or via the prefrontal cortex (Condé et al., 1995; Hurley et al., 1991).

3. Intrinsic inhibitory mechanisms that control propagation across rhinal cortices

Considering the evidence reported above, it should be concluded that propagation of activity between PRC and ERC, occurs with an extremely low probability. As a result, the rhinal cortices may be considered as a filter or a gate that controls bi-directional transfer of information between neocortex and hippocampus. In this section, we consider the network mechanisms that control impulse traffic through rhinal cortices.

Direct neocortical stimulation in slices of the perirhinal region kept *in vitro* evokes different responses depending on both the orientation of the slice cut and the location of the recorded neurons. In coronal slices, neocortical as well as ERC and PRC stimuli were reported to evoke an isolated monosynaptic EPSP mediated by glutamatergic neurotransmission in area 35 principal neurons (Ziakopoulos et al., 1999; Cho et al., 2000). More recent studies demonstrated that in coronal slices, neocortical stimuli also evoke large GABAergic synaptic potentials (Martina et al., 2001b) and currents in PRC neurons (Garden and Kemp, 2002).

The effect of neocortical stimuli in horizontal PRC slices depends on the rostrocaudal distance between neocortical stimulation site and recorded perirhinal neuron. Indeed, stimulation sites located at the same rostrocaudal level as the recorded cells evoke EPSP–IPSP sequences whereas distant neocortical stimulation sites evoke apparently pure excitatory responses (Fig. 3; Martina et al., 2001b). These results suggest that neocortical inputs not only target principal perirhinal cells but also recruit inhibitory interneurons located at the same transverse level, whose activation limits the depolarization of principal neurons. In contrast, distant

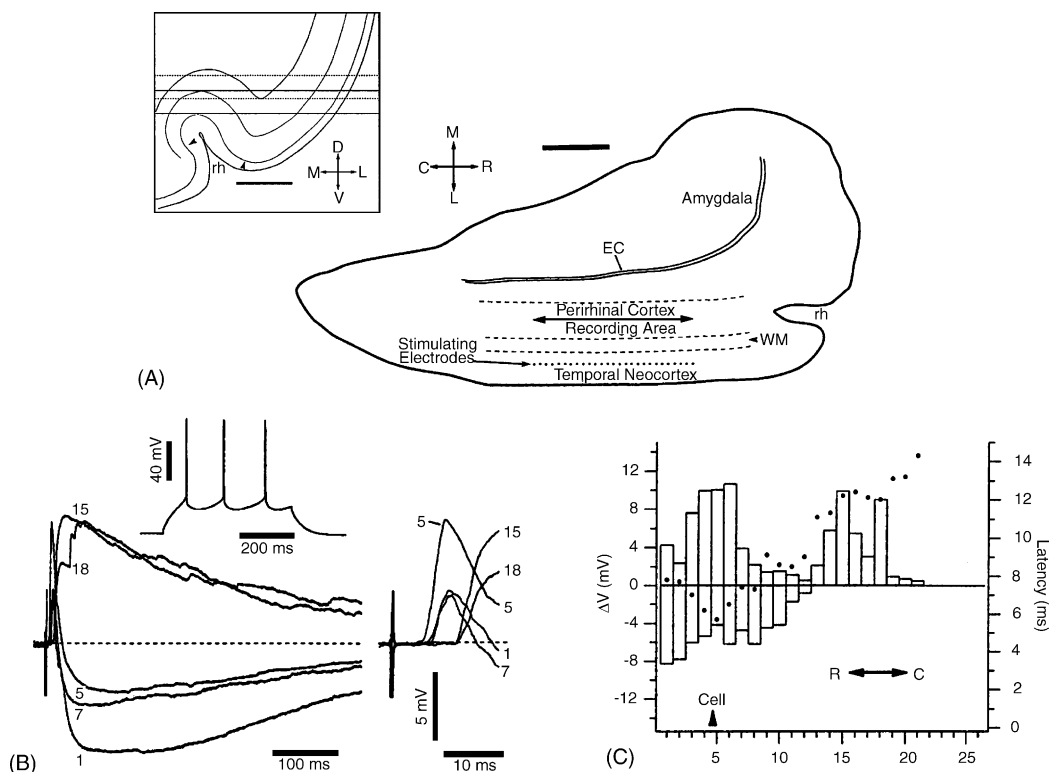


Fig. 3. Response profile of a PRC cell to NC stimuli applied at different rostrocaudal levels. (A) horizontal slice of the rat PRC, as it appeared in the recording chamber (EC, external capsule and WM, white matter). The continuous and dashed horizontal lines in the inset on the left depict the cortical region utilized for horizontal sections. (B) Synaptic responses to electrical stimuli (100 μs; 1.4 times the threshold intensity) applied in the neocortex at multiple sites 160 μm apart. The inset illustrates the first response to depolarizing current injections eliciting more than one spike when current injections were increased in steps of 0.01 nA from rest. Synaptic responses elicited by selected stimulation sites (numbers) depicted with a slow (left panel) and fast (right panel) time base are shown. The positions of the stimuli (1–27) are reported in the x-axis of panel (C), where graphs plotting the peak amplitude (bars, left axis) of evoked synaptic potentials as a function of the stimulation site are illustrated (average of four responses). The onset latency of the EPSPs is also indicated (dots, right axis). The position of the recorded cells with respect to the stimulation sites is indicated by a triangle at the bottom of each graph. Calibration bars in A = 1 mm. Modified from Martina et al., 2001b.

neocortical inputs only evoke excitation, because longitudinal perirhinal pathways do not engage inhibitory interneurons.

Results obtained in the isolated brain preparation with simultaneous current-source density analysis and intracellular recordings confirm and extend these observations (Biella et al., 2001). Stimulation of both the temporal neocortex and the PRC at the same rostrocaudal level as the intracellularly recorded layer II–III perirhinal neuron reveals large amplitude biphasic IPSPs that curtail the monosynaptic EPSPs and prevent neuronal firing (Fig. 4A; Biella et al., 2001). In fact, neocortical as well as local area 36 stimuli seldom induced neuronal discharge in PRC cells. Neuronal firing could be induced by low-intensity local stimulation in PRC by increasing stimulus intensity action potential firing was suppressed by the gradual development of a biphasic IPSP (Fig. 4A). The absence of neuronal firing and the short time to onset of the IPSP in principal cells strongly suggest that a powerful feed-forward inhibitory circuit is activated by the incoming stimulus (Biella et al., 2001). Field potential laminar analysis performed during intracellular recordings from principal neurons demonstrates that the generators responsible for the neocortical-PRC network interactions are localized in superficial layers (Biella et al., 2001). Similar laminar responses were also observed in area 35 after either neocortical or area 36 stimulation, suggesting that analogous network interactions may operate in this PRC subfield.

In PRC slices, local electrical stimuli applied in the presence of glutamate receptor antagonists evoke biphasic IPSPs mediated by GABA-a and GABA-b receptors, respectively, in principal neurons (Martina et al., 2001a). In contrast, only short-lasting GABA-a responses are evoked in fast-spiking interneurons (Martina et al., 2001a). Moreover, in perforated patch recordings, using the cation-selective ionophore gramicidin, the reversal potential of GABA-a responses is much closer to spike threshold in interneurons (-54 mV) than in projection cells (-72 mV).

Pharmacological analyses revealed that this difference arises from cell-type-specific chloride homeostatic mechanisms that accumulate chloride in interneurons and extrude chloride in projection cells (Martina et al., 2001a). This suggests that in the PRC, fast-spiking interneurons are more excitable than principal cells, not only by virtue of their dissimilar electroresponsive properties but also because they express a different complement of GABA receptors and chloride homeostatic mechanisms.

The efficient control of neuronal firing established within the PRC suggests that the mechanisms that regulate the propagation of neocortical activity to the hippocampus reside in this cortical region. Nevertheless, the possibility that entorhinal neurons also contribute to gate activity propagation has to be considered. Feed-forward inhibition that prevents entorhinal neurons from reaching spike threshold has been reported in vivo (Finch et al., 1988). Pronounced IPSPs that hinder neuronal firing have also been described in vitro in superficial principal neurons (Funahashi and Stewart, 1998; Jones, 1994), whereas deep layer cells in slices respond to afferent and local stimulation with EPSPs that are not followed by inhibitory potentials (Glovelli et al., 1997; Jones and Heinemann, 1988). The picture emerging from these observations is that, as for PRC, entorhinal principal neurons are low-excitability elements that have a low probability of firing in response to synaptic activation. This hypothesis is reinforced by the demonstration that olfactory-driven activation of superficial and deep cells respectively in the medial and lateral ERC of the isolated guinea pig brain is not followed by PRC invasion (Fig. 2b; Biella et al., 2003).

What is the significance of the low probability perirhinal transfer of neocortical and entorhinal inputs? We submit that the solution resides in the particular cell types involved in the stepwise progression through the rhinal cortices. As was mentioned above, the progression of impulses through discrete steps (neocortex to area 36 to area 35 to ERC and

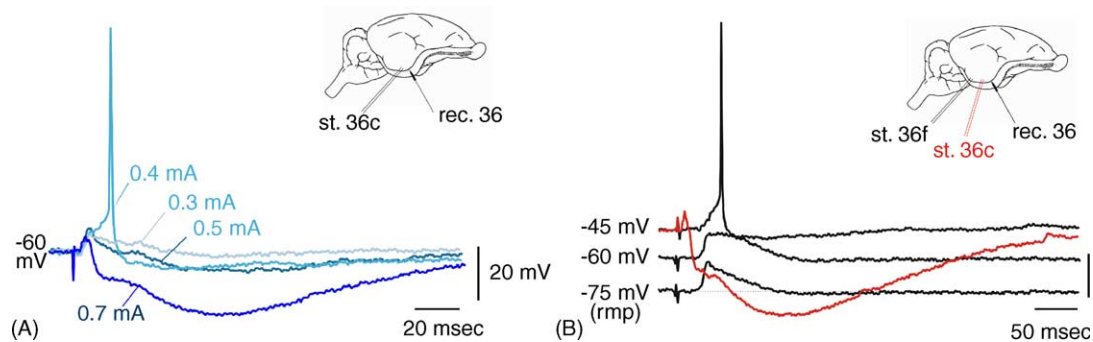


Fig. 4. PRC neuronal firing is controlled by feed-forward IPSPs. Intracellular recordings from PRC neurons (area 36) recorded in the isolated guinea pig brain preparation. (A) Low intensity local PRC stimulation promotes neuronal firing (0.4 mA). Further intensity increase (0.5–0.7 mA) reveals a fast onset, biphasic IPSP that prevents action potential generation. (B) Local stimulation of the PRC in a position close to the recorded cell (st. 36c) evokes a brief EPSP followed by a feed-forward IPSP (red line). Stimulation at a site remote from the cell (far 36 site: st. 36f) induces an EPSP, whose duration is elongated during membrane potential depolarization (black lines). When the threshold for spike generation is reached, only a small-amplitude post-spike repolarization was observed (from Biella et al., 2001).

conversely) is not perfect, as some neocortical neurons project beyond area 36 into area 35 and the lateral EC and some entorhinal axons extend to area 35 and the temporal neocortex (see references above). Thus, propagation through the rhinal cortices occurs in two ways: most of the connections involve a relatively slow step-wise progression through a sequence of cortical areas, but a minor proportion of axons “jump ahead”. We hypothesize that the latter originate either in (1) GABAergic cells that contact principal neurons or (2) in glutamatergic cells that mainly contact GABAergic interneurons. As this second mode of communication is faster than the prevalent step-wise propagation, GABAergic IPSPs generated by the fast route will precede EPSPs generated by the slow path. As a result, the probability of transfer through the slow path will be severely reduced. However, these predictions await testing with tract-tracing coupled to GABA immunocytochemistry at the electron microscopic level.

The importance of inhibition in the control of rhinal excitability revealed with physiological techniques is corroborated by the analysis of the distribution of GABAergic neurons in the rhinal cortices (Wouterlood, 2002). Antibodies against the GABA synthesis enzyme, glutamic acid decarboxylase, stain a large number of neurons and terminals in superficial ERC layers II and III (Miettinen et al., 1997; Kohler et al., 1985). The calcium-binding proteins calbindin and parvalbumin are also strongly expressed in neurons and terminals of the superficial ERC layers (Suzuki and Porteros, 2002; Miettinen et al., 1997; Mikkonen et al., 1997; Fujimaru and Kosaka, 1996; Tunon et al., 1992), whereas calretinin was observed in both GABAergic and putative non-GABAergic ERC cells (Wouterlood et al., 2000). In comparison to ERC, lower concentrations of parvalbumin and calbindin positive cells and terminals (Suzuki and Porteros, 2002; Fujimaru and Kosaka, 1996) and a more intense calretinin staining (Wouterlood et al., 2000; Miettinen et al., 1997) were observed in the PRC. In particular, parvalbumin-positive terminals show an abrupt reduction at the border between ERC and PRC (van Groen, 2001; Wouterlood et al., 1995; Tunon et al., 1992). These observations suggest that the distribution of inhibitory neurons and fibers/terminals has a peculiar arrangement in rhinal cortices, characterized by a denser immunoreactivity for GABA, GAD and calcium-binding proteins in superficial layers (Wouterlood, 2002).

The critical question is whether the inhibitory control of perirhino-entorhinal communication is ever lifted and if so, how. Recently, it was reported that amygdala inputs could promote the spread of perirhinal activity to the ERC and hippocampus in conditions of partial GABA-A block (Kajiwara et al., 2003). Thus, it is conceivable that afferents to the rhinal cortices, by reducing inhibition, might facilitate impulse traffic in this circuit. While the identity of these afferents remains unknown, likely possibilities include the medial prefrontal cortex and the basolateral amygdala, which sends a glutamatergic projection to the PRC and ERC

(Allt and Lawrenson, 2000; Room and Groenewegen, 1986; Krettek and Price, 1977a,b; Takagishi and Chiba, 1991; Sesack et al., 1989). In light of recent findings implicating both regions in the control of reward-related behavior and emotions (Baxter and Murray, 2002; Ongur and Price, 2000; Aggleton et al., 2000), these results suggest that impulse traffic through rhinal cortices will vary depending on the emotional significance of current environmental contingencies.

How could glutamatergic axons from the prefrontal cortex or amygdala overcome the inhibitory pressures of the rhinal cortices? At the simplest level, these extrinsic glutamatergic inputs might overcome the local inhibition by causing a sufficient depolarization of projection cells. Another possibility is that they activate a subgroup of GABA interneurons that inhibit other GABA cells, as demonstrated for the hippocampus, where calretinin-positive hippocampal interneurons only contact other interneurons (Gulyas and Freund, 1996). As a result, excitatory afferents to these local circuit cells would produce a disinhibition of principal projection cells.

Yet another unexplored scenario is the possibility that the intrinsic membrane properties and electrotonic structure of principal cells and interneurons conspire to allow certain combinations of activity patterns to “open the gate”. Rather than overcome the local inhibition, these activity patterns might make use of the tendency of interneurons to self-organize in oscillatory states that dynamically recruit and pace projection cells. Much evidence of such dynamical processes has been recently obtained in other cortical areas (Buzsáki et al., 2004; Buzsáki and Draguhn, 2004).

4. Associative longitudinal propagation of excitation within PRC and ERC

The results reviewed above strongly suggest that a wall of inhibition, represented by network interactions within rhinal cortices, controls and regulates the reciprocal transfer of information between neocortex and hippocampus. In contrast with the low probability transfer seen in the transverse direction, activity propagates efficiently in the longitudinal axis along connections that span the entire rostro-caudal extent of longitudinal bands of rhinal cortex, running parallel to the rhinal fissure (Burwell and Amaral, 1998a). Intracellular studies *in vitro* demonstrated that the activation of such a longitudinal fiber system generates large-amplitude excitatory responses that hardly ever evoke neuronal firing (Martina et al., 2001b; Biella et al., 2001). When action potential threshold is attained, as for instance after membrane potential depolarization by an intracellular current pulse, small amplitude inhibitory potentials of short duration are observed (Biella et al., 2001), suggesting that at least in area 36 neurons, feedback inhibition is not prominent (Fig. 4B). As for PRC, extensive longitudinal associative connections with a prominent longitudinal

direction have been described in the ERC (Biella et al., 2002b; Dolorfo and Amaral, 1998).

We propose that these longitudinal associative connections can merge coincident patterns of activation (EPSPs) mediated by separate inputs of neocortical origin that converge into the PRC (or into ERC). The summation of concurrent EPSPs could promote neuronal firing in a small population of cells that will transfer excitation to the next synaptic station toward the hippocampal formation. A similar progression of events could govern the reciprocal propagation of neuronal activity from the hippocampus to the neocortex. This transfer may be facilitated in particular functional states of the parahippocampal cortex, such as during the generation of theta or gamma oscillatory activity (Collins et al., 2001; Dickson et al., 2000; van der Linden et al., 1999; Chrobak and Buzsáki, 1998). Indeed, we recently demonstrated that carbachol-induced gamma oscillations are transiently reset and synchronized by synaptic co-activation of remote ERC sites that show low coherence before stimulation (Dickson and de Curtis, 2002). This mechanism may provide temporal and spatial relevance (Hebbian reinforcement) to specific inputs through the enhancement of neuronal synchronization and firing of ERC neurons.

5. Implication for the genesis and propagation of epileptiform activity

Failure of the inhibitory control that usually dominates interactions between PRC, ERC and hippocampus may lead to permanent excitability changes that will promote limbic epileptogenesis. For instance, it has been demonstrated that propagation of olfactory-driven activity from the ERC to the PRC is facilitated in conditions of hyperexcitability, such as after kindling (Kelly and McIntyre, 1996; McIntyre and Plant, 1993) and during applications of GABA-receptor antagonists in the ERC, close to the rhinal sulcus (Federico and MacVicar, 1996; Biella et al., unpublished observations). In vivo and in vitro experimental reports demonstrated that disinhibition of ERC evokes ictal discharges that secondarily entrain the dentate gyrus and promote the re-entrant activation of the ERC–hippocampal–ERC loop, therefore facilitating the initiation of self-sustained epileptiform activity (Paré et al., 1992; Lothman et al., 1991). In combined entorhinal and hippocampal slices, seizure-like activity is generated primarily in ERC and PRC and from there propagates to the hippocampal subfields CA1 and CA3 (de Guzman et al., 2004; Avoli et al., 2002). Moreover, experimental and human studies in temporal lobe epilepsy demonstrated a selective depletion of layer III neurons in the ERC (Du et al., 1995, 1993), that may facilitate reentrant activation of the hippocampal–ERC loop via disinhibition of local networks in CA1 (Empson and Heinemann, 1995).

Inspired by these experimental indications, the focus of clinical studies on human temporal lobe epilepsy has shifted

from the hippocampus to the parahippocampal region. The analysis of extra-hippocampal temporal cortices with magnetic resonance, indeed, demonstrated that in patients with temporal lobe epilepsy the ERC and the parahippocampal region can be markedly reduced in volume (Bernasconi et al., 1999, 2003; Jutila et al., 2001; Klueva et al., 2003) even in the absence of a clear radiological pattern of mesial temporal sclerosis, typically associated with a selective hippocampal damage (Sloviter, 1994; Babb, 1991). The above findings suggest that changes in excitability and network interactions in the ERC (and possibly in the PRC) may precede the involvement of the hippocampus proper during the development of temporal lobe epilepsy.

6. Conclusions

The studies reviewed above delineate a new functional organization of the rhinal cortices, according to which transverse propagation of activity from the neocortex to the hippocampus via PRC and ERC is hindered by a powerful inhibitory control, whereas longitudinal propagation within both PRC and ERC is not. In keeping with this view, information transfer from the neocortex to the hippocampus (and vice-versa) may occur through the integration of coincident events within each band of rhinal cortices parallel to the rhinal sulcus (area 36, area 35, lateral EC) and, at subsequent level, via propagation across different cortical bands (Fig. 5). Therefore, the key to understand reciprocal information flow between neocortex and hippocampus may reside in the amplification and selection of activity patterns along longitudinal associative connections, perhaps via coincidence detection and/or extrinsic control by extratemporal brain regions. The proposed model is consistent with memory consolidation and retrieval functions that require selective and precise integration of memory elements that enter and leave the hippocampal formation.

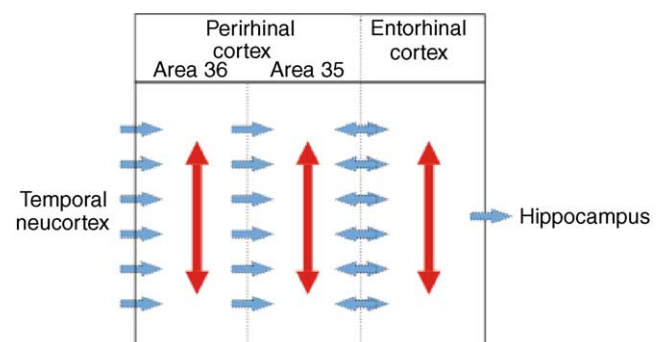


Fig. 5. Summary of the reciprocal information flow from the neocortex to the hippocampus, through rhinal cortices. Propagation of excitation along associative fiber systems within each cortical subregion is marked by vertical red arrows. The propagation across parahippocampal subregions controlled by local inhibition is depicted by blue arrows.

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