# Gating neuronal activity in the brain

*Cellular and network processing of propagating activity in the perirhinal–entorhinal cortex*

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GENERAL DISCUSSION

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# Main findings

I. Cortical insular (AiP) as well as subcortical lateral amygdala (LA) input activates the PER-LEC neural network, however in a different fashion. The LA activates neurons in the deep layers and the AiP input activates neurons in the superficial layers first. Once inhibition is slightly reduced, the activity spreads through the network (Chapter 2).

II. AiP input is received by superficial and deep layer principal neurons and consists of a small excitatory and large inhibitory response which regulates neuronal output. PV interneurons in the local PER-LEC network are responsive to direct AiP input by action potential firing, creating a strong inhibitory response in principal neurons (chapter 3 and 4).

III. Superficial layer neurons are receive stronger synaptic input and are more responsive to AiP synaptic input than deep layer neurons, as they show more action potential firing in response to stronger synaptic input (chapter 4).

IV. The timing and amplitude of the excitatory and inhibitory input is different in superficial and deep layer neurons, creating a net excitation which is more favorable for action potential firing in superficial than in deep layer neurons (chapter 4).

V. The AiP and LA inputs interact mainly in the inhibitory network in the PER-LEC deep layers. Interaction of the AiP and LA inputs evokes earlier PV interneuron firing and the resulting inhibitory response in principal neurons is evoked earlier (chapter 5).
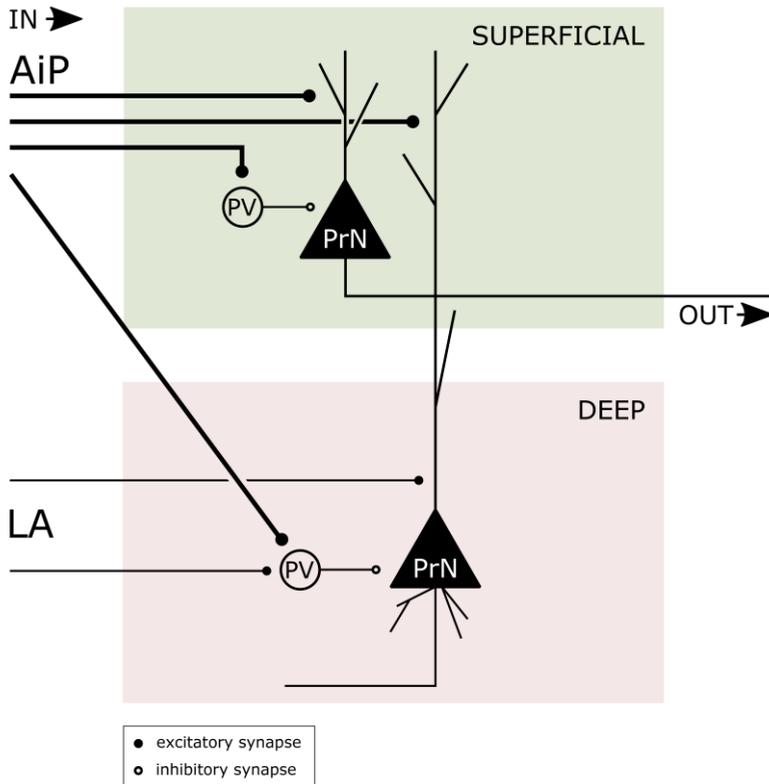
**Figure 6.1.** *Schematic overview of the PER-LEC network examined in this thesis.*

Input from the neocortical agranular insular cortex (AiP) projects strongly onto superficial layer principal neurons (PrN) and the dendrites of deep layer principal neurons. The AiP also projects directly onto parvalbumin expressing (PV) interneurons in both layers, which provide the inhibition in principal neurons. The lateral amygdala (LA) projects directly onto deep layer principal neurons as well as PV interneurons, however the strength of the projection is less than for the AiP projection.

The superficial layer neurons provide output in this network by responding to AiP input with action potential firing, whereas deep layer neurons remain silenced by inhibition.

The mechanism of information processing by the parahippocampal region is still largely unknown. The results in this dissertation answer the fundamental question how a subdivision of the parahippocampal region, the perirhinal (PER) and lateral entorhinal (LEC) cortex, handles incoming neuronal activity and how this activity can be modulated before transmission towards the hippocampus. I will discuss the aspects of information processing in the PER-LEC network as known from the literature and relate these findings to my own results. The emphasis will be on the synaptic input received by PER-LEC excitatory and inhibitory neurons and how these neurons respond to this input with action potential firing.

### The perirhinal-entorhinal gate

*Functional connectivity in the PER-LEC network*

The PER-LEC network forms the main input-output structure for the hippocampus (Cappaert, Van Strien, & Witter, 2014). It is generally assumed that information travelling towards the hippocampus is mainly transmitted via the superficial layers of the PER-EC network (Ruth, Collier, & Routtenberg, 1988; Witter, 1993) and that the deep layers return the information from the hippocampus to the neocortical areas (Buzsáki, 1996; Canto, Wouterlood, & Witter, 2008). This input-output structure is crucial for memory formation since it has been shown that degeneration of the PER-LEC network results in early memory loss in Alzheimer's patients (Krumm et al., 2016). Activity transfer through the PER-LEC network occurs with a low probability (Biella, Uva, & de Curtis, 2002; Pelletier, Apergis, & Paré, 2004; Willems, Wadman, & Cappaert, 2016), indicating that the PER-LEC network, instead of being a simple relay station, plays a role in the selection of relevant information for further hippocampal processing (de Curtis & Paré, 2004). The question however is, if the probability of activity transmission is low because the synaptic inputs are not sufficient to evoke action potential firing or if the generation of action potentials is hindered.

The projections from many cortical structures target the superficial layers of the PER-LEC network: anatomical data showed that the cingulate, orbitofrontal and insular cortex project to the perirhinal and entorhinal cortex and olfactory areas project to the entorhinal superficial layers, whereas hippocampal areas project to the deep layers (Deacon, Eichenbaum, Rosenberg, & Eckmann, 1983; Kerr, Agster, Furtak, & Burwell, 2007; Room & Groenewegen, 1986). The PER has many associational connections and is therefore assumed to be an integration structure which processes information before the PER provides its input to the EC (Insausti, Amaral, & Cowan, 1987; Lavenex & Amaral, 2000). In this dissertation we focused on the synaptic input from the agranular insular cortex (AiP), a neocortical afferent of the PER-LEC. We do expect that other cortical areas recruit the PER-LEC network in a comparable way, based on the resembling anatomical projection sites of these areas. It is therefore hypothesized that information from different cortical areas is combined by neurons in the PER-LEC network and afterwards transmitted to the hippocampus.

Furthermore, projections from the cortex are rostrocaudally organized in the PER-LEC network (Room & Groenewegen, 1986). This anatomical organization supports rostral to

caudal propagation of neocortical inputs through the PER (Biella, Uva, & Curtis, 2001; Martina, Royer, & Paré, 2001). In line with these findings, we showed in chapter 2 that this organization results in a sequential activation of the PER-LEC network was organized longitudinally along the rostrocaudal axis.

Information from the cortex is likely carried and passed along by assemblies of synchronously active neurons, not by single neurons (Abeles, Prut, Bergman, & Vaadia, 1994). Synchronized activity of groups of neurons is therefore considered an important feature of activity transmission, since target structures, such as the hippocampus, can efficiently detect and respond this synchronous activity (Salinas & Sejnowski, 2001). These synchronous neuronal firing patterns of these active neurons code the information in the spike-timing and spike-count (Quian Quiroga & Panzeri, 2009). The timing of evoked synaptic input and the spike patterns resulting from this input are addressed in this dissertation by examining how a single input activates neurons in the PER-LEC network. In this way, the timing of the neuronal activity can be compared between groups of neurons in different brain areas, to address how information is processed in the network. The rate-coding of neurons is best studied by evoking patterns of synaptic input by stimulus trains, which is not done in this dissertation, but could well play an equal role in activity transmission between brain areas.

In chapter 3 and chapter 4 we showed how the two separate layers of the PER-LEC, the superficial layer I-III and the deep layers V-VI, are activated by the AiP synaptic projections. The principal neurons in the superficial layers receive stronger synaptic input which results in more action potential firing, probably forming a larger assembly of active neurons as a response to synaptic input. The synaptic input received by the deep layer neurons is smaller, resulting in a very small group of firing neurons. It is hypothesized that superficial layer neurons provide information to the hippocampal circuit. The small input in deep layer neurons is thought to provide a copy of the information which is transmitted to the hippocampus. This input is likely received by deep layer neurons through monosynaptic connections which superficially target the large dendritic tufts of the deep layer neurons or di-synaptic through the extensive intrinsic connectivity between the superficial and deep layers (Witter, Doan, Jacobsen, Nilssen, & Ohara, 2017).

In addition, the deep layer population receives strong, feedforward inhibition, suggesting that this network does not have the function to transmit cortical activity to the hippocampus. This indicates that the superficial layers can carry information, in the form of action potential firing (chapter 4), towards the hippocampus whereas the deep layer output network is actively silenced by strong feedforward inhibition (chapter 3). These findings are in line with data of de Villers-Sidani and colleagues (2004) showing that there is a separated bidirectional pattern of synaptic interactions in the superficial and deep layers of the PER-LEC network (de Villers-Sidani, Tahvildari, & Alonso, 2004). The concept of the regulation of this bidirectional pattern is found for the return transmission of activity from the hippocampus back to the cortex through the deep layer output network as well: activity transfers via the deep entorhinal layers whereas at the same time superficial layer neurons are actively inhibited (Gnatkovsky & de Curtis, 2006).

Our studies were conducted in a slice preparation, known for their relatively quiescent state compared to the *in vivo* high conductance state (Destexhe, Rudolph, & Paré, 2003). It is therefore possible that when recorded *in vivo*, the fluctuating conductance states in both

superficial and deep layer neurons make the principal neurons more prone to action potential firing (Destexhe et al., 2003). Nevertheless, if we assume that the principal neurons and inhibitory neurons are both affected by the quiescent state, the difference in the excitatory-inhibitory responses evoked by neocortical input would still result in a larger population of firing neurons in the superficial layers compared to the deep layers.

*The role of inhibition in the gating mechanism of the PER-LEC network*

An important role for the inhibitory network in actively selecting and regulating relevant information through the PER-LEC network has been proposed (de Curtis & Paré, 2004). Nevertheless, the exact role of inhibitory neurons in the gating of activity is not yet clear. The inhibitory responses evoked by cortical input originate in the local network (Martina et al., 2001). Transmission of activity through the PER to the LEC is strongly hindered by this local network inhibition: if the inhibition is reduced by a competitive GABA$_A$ receptor blocker, activity consequently progresses through the PER to the LEC, indicating that activity is reliably transmitted (Biella, Spaiardi, Toselli, de Curtis, & Gnatkovsky, 2010; Willems et al., 2016); chapter 2). Furthermore, excitatory connectivity between principal neurons in the LEC

superficial layers is sparse, but principal neurons are mainly connected di-synaptically via inhibitory interneurons (Nilssen et al., 2018), indicating a major role for the interneuron population in entorhinal processing.

The inhibitory response is a result of activity of GABAergic interneurons. As described in the general introduction, various types of interneurons are present in the PER-LEC network, including calbindin, calretinin, somatostatin, 5HT3r, and parvalbumin expressing interneurons (Barinka et al., 2012; Leitner et al., 2016; Rudy, Fishell, Lee, & Hjerling-Leffler, 2011). It is not known whether these different types of interneurons have a specific function in the PER-LEC network. The exact role of most types in the regulation of activity transmission in PER-LEC network still remains to be examined and in chapter 3 and chapter 4 we addressed the role of the PV interneurons. These interneurons were chosen since they are known for their projection onto the axo-somatic site of the principal neuron, hence they can evoke large inhibitory responses upon activation (Pfeffer, Xue, He, Huang, & Scanziani, 2013). We showed that superficial and deep layer PV interneurons receive a strong synaptic input compared to principal neurons (chapters 3, 4 and 5). This larger synaptic input can be due to the presence of more and larger glutamatergic terminals on interneuron dendrites, resulting in more effective activity transmission in interneurons (for review see Buzsáki, Kaila, & Raichle, 2007). This effectivity fits neatly with the action potential firing patterns which were evoked in PV interneurons after AiP stimulation (chapters 3 and 4). Although many other GABAergic interneurons might be active in the PER-LEC network, we showed that PV interneuron firing is highly correlated with the evoked inhibitory synaptic response in the simultaneously recorded principal neurons in both superficial (chapter 4) and deep (chapter 3) layers. Furthermore, PV interneurons receive their synaptic input earlier than principal neurons which indicates that PV interneurons are directly activated in a feedforward manner (chapters 3 and 4). This is supported by anatomical data showing a high incidence of glutamatergic synapses from the PER to EC GABAergic neurons (Pinto, Fuentes, & Paré, 2006).

The inhibition recruited in the PER-LEC network clearly effectively silences the deep layer principal neurons. However, the question still remains what the role of this strong inhibition is in transmission of activity. The regulation of principal neuron firing by PV interneurons as shown in chapter 4 can be the underlying mechanism of this gate. In networks where

excitation and inhibition are balanced, only slight differences in the timing and amplitude of the excitation or inhibition can open and close the gate for transmission of activity (Vogels & Abbott, 2009). This study showed that the time and amplitude relation between excitatory and inhibitory input – the excitability ratio – evoked in principal neurons creates a window of opportunity for spiking, refining the spike-timing and therefore carrying information for downstream information transfer. This gating mechanism depends on two aspects: 1) the accuracy of PV interneuron firing and 2) the timing and amplitude of the excitatory input. In chapter 3 and 4, PV interneurons respond very accurately after receiving synaptic input, ensuring very consistently timed, reliable inhibition of principal neurons. This reliable inhibition blocks principal neuron firing if excitatory input is received too late or not strong enough. It seems that only when the timing of excitation is early enough and the excitatory input is large enough, the principal neuron spikes before the accurately timed inhibition emerges. The regulation of PV interneuron accuracy and the timing of excitation in principal neurons results in synchrony of principal neuron firing in the network. By means of synchronous ensemble activity in the PER-LEC network, highly relevant information can be conducted to the hippocampus where an ensemble representation specific for the current information is formed (Pennartz, Uylings, Barnes, & McNaughton, 2002).

### Integration of information in the PER-LEC network

*Integration of activity in neural networks: combining input from multiple brain areas*

Interaction of synaptic inputs is often studied *in vivo* on the level of crossmodal brain regions where integration of multiple sensory inputs takes place. These areas combine information from multiple senses, for example visual and tactile information, and increase stimulus detection (Stein & Stanford, 2008). The interplay between excitatory principal neurons and inhibitory interneurons is crucial for multisensory integration. For example, if a multimodal network receives multiple inputs from visual and somatosensory primary areas, inhibitory neurons do not alter their firing rates whereas principal neurons increase their firing rate (Olcese, Iurilli, & Medini, 2013). An explanation for this phenomenon could be that principal neurons are more sensitive to synaptic input variation, and can therefore vary their firing rate, whereas varying synaptic input received by interneurons is not translated into an altered spike pattern. How synaptic input interacts in integration areas and which

**Box 3 | Synaptic integration**

Individual neurons integrate thousands of synaptic inputs they receive to generate an output: action potential firing. The complex geometry of dendrites and their synaptic connections, together with the active and passive dendritical properties allow complex computation of multiple sources of input. Eventually the output, i.e. action potential firing, is initiated near the soma in the axon initial segment (Shu, Duque, Yu, Haider, & McCormick, 2007), indicating that how effective synaptic input is transmitted to the axon initial segment determines how the synaptic input can influence the neuronal firing pattern (Stuart & Spruston, 2015).

Synaptic integration in single neurons comes in various forms: 1) integration of synaptic input on multiple dendrites, where synchronized activity of the input generates a dendritic spike, 2) the enhancement of distal synaptic input by proximal dendritic spike initiation, 3) integration of inhibitory and excitatory synaptic input on the dendrites, where inhibition can veto the more distal excitatory input, and 4) the integration of synaptic inputs from multiple brain areas on the various sides of the neuron where the dendrite functions as a coincidence detector (Stuart & Spruston, 2015). These forms of integration all play a role in processing of input before spike patterns are evoked and activity is transmitted onto the postsynaptic neuron.

Additionally, not every synaptic input should be conducted into an action potential, since action potential firing is a large energy investment. It has been shown that the size of the postsynaptic current is set to not always transmit information, since the information transmitted per used energy is optimized (Harris, Jolivet, Engl, & Attwell, 2015). If synaptic inputs induce maximal postsynaptic currents, the information transfer is much higher, but the information per energy used is much lower. Synaptic input onto different dendritic compartments can therefore be sub maximal (and energy efficient), but be integrated at the soma to be transmitted in an energy efficient way to the next, postsynaptic neuron.

consequences this interaction had for the firing of principal neurons and interneurons is not yet clear. The interaction of synaptic inputs depends on various features like the intrinsic properties of the receiving neuron and the spatial distribution of synaptic contacts (Box 3). In this dissertation we addressed the interaction of synaptic inputs in the PER-LEC network by examining the behavior of principal neurons and PV interneurons in response to synaptic input from two distinct brain areas.

*The PER-LEC network as an integration area*

Information from several neocortical areas travels towards the hippocampus for memory consolidation and is relayed by the PER-LEC network (Buzsáki, 1996; Pennartz et al., 2002). In addition to the many cortical areas projecting to the PER-LEC network as described above, the PER-LEC receives afferents from many subcortical brain structures such as the lateral amygdala, raphe nuclei, claustrum, brain stem, basal forebrain, thalamus, and hypothalamus (Deacon et al., 1983; Finch et al., 1986; Insausti et al., 1987). The presence of these connections suggests that the PER-LEC network is able to integrate many sources of input, before activity is transmitted towards the hippocampus. This makes the PER-LEC a crucial structure where input from various cortical and subcortical areas can interact and where transmission to the hippocampus can be regulated.

Interaction of synaptic inputs and activity in the rhinal cortices plays an important role in controlling memory function. For example, inhibitory control of activity in the rhinal cortices by synaptic input from the prefrontal cortex impedes memory retrieval when a certain memory has to be suppressed (Anderson, Bunce, & Barbas, 2016). This inhibition is most

likely achieved by direct excitatory projection activating local network parvalbumin expressing inhibitory neurons (Apergis-Schoute, Pinto, & Paré, 2006; Bunce, Zikopoulos, Feinberg, & Barbas, 2013). It is suggested that rhinal quiescence could serve as a functional process in suppression of memory retrieval (for review see Depue, 2012). These studies showed that interaction of rhinal achtivity and synaptic input from modulating brain areas can ultimately regulate memory function in humans.


*Modulation of cortical input by amygdala activity*

The amygdala is considered an emotion-related brain area (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; LeDoux, 2012). Emotional enhancement of information processing by the amygdala is an important aspect of the memory system. Fear memory is impaired when the projection from the basolateral amygdala to entorhinal cortex is inhibited, indicating that input from the amygdala can modulate memory function in the entorhinal cortex (Sparta et al., 2014). Furthermore, it is shown that the information from the amygdala and the neocortical areas can modulate the medial temporal lobe activity (including the PER and LEC) and therefore enhance memory performance of emotional stimuli in humans (Dolcos, LaBar,

& Cabeza, 2004). The underlying mechanism of the increased memory performance at emotional stimuli is studied both *in vivo* and *in vitro* by addressing the modulation of PER-LEC activity by LA input. BLA activity facilitates neuronal interactions in the rhinal cortices during emotional memory formation *in vivo* (Paz, Pelletier, Bauer, & Paré, 2006) and in slices, amygdala input promotes progression of PER activity to the entorhinal-hippocampal circuit (Kajiwara, Takashima, Mimura, Witter, & Iijima, 2003; Koganezawa et al., 2008). In chapter 2 we showed that stimulation of the AiP leads to activation of the PER-LEC network in a rostral to caudal manner, whereas the LA evokes initial responses mainly in the PER-LEC deep layers. This pattern of network activation enables that, only if activity of the PER-LEC network and the LA coincides in the LEC deep layers, the activity is transmitted to the dentate gyrus of the hippocampus when the inhibition is slightly reduced (Koganezawa et al., 2008).

Transmission of synaptic input relies on whether the synaptic input evokes action potential firing in the postsynaptic neuron. This synaptic input is received by the neuronal dendrites and is integrated in various ways to eventually evoke the action potential firing pattern that contains the computed information received by the dendritic tree (Box 3). The interaction of AiP and LA synaptic inputs in the excitatory and inhibitory components of the PER-LEC network was examined in chapter 5 at the cellular, microcircuit and network level. We first compared the interaction properties of the excitatory and inhibitory conductances in principal neurons and found that the excitation was summated sublinearly. The fact that the evoked excitatory conductance was not summed could be due to the activation of inhibitory terminals on the excitatory synapses, the so called pre-synaptic inhibition. Although it is not yet known whether pre-synaptic inhibition plays a role in the decrease of excitatory conductance after simultaneous stimulation of the AiP and LA in PER-LEC principal neurons, this phenomenon has been shown in the olfactory system. Interneurons can provide presynaptic inhibition of excitatory synapses in olfactory sensory neurons (McGann, 2013), leading to decrease in excitatory responses recorded post-synaptically.

Unlike the excitatory conductance, the evoked the inhibitory conductance did summate linearly. In accordance with this, the synaptic input in PV interneurons summated linearly as well, although the amount of output of the PV interneurons, assessed by the number of spikes, did not change. However, the inhibitory response in the principal neuron as well as the first evoked spike in the PV interneurons was evoked earlier after simultaneous

stimulation of AiP and LA. Three sources of inhibition could account for this fast inhibitory control of the simultaneous synaptic input: 1) direct inhibitory projections from the amygdala to the PER-LEC region (McDonald & Zaric, 2015), 2) direct inhibitory projections from the AiP (Pinto et al., 2006) and 3) fast recruitment of PV interneurons in the local PER-LEC network. Although direct inhibitory projections from neocortical areas and the amygdala have been shown anatomically (McDonald & Zaric, 2015; Pinto et al., 2006), it is unlikely that we stimulated these inhibitory projections in our slice preparation, since complete blockade of glutamatergic transmission abolished the inhibitory responses after AiP (Willems, Wadman, & Cappaert, 2018) and LA stimulation (chapter 5). It is thus plausible that, in the current experimental set up, inhibition in the principal neurons is evoked by the firing of local PV interneurons (chapter 5), which are known for their clustered somatic and axo-axonic projections onto principal neurons (Wouterlood, Härtig, Brückner, & Witter, 1995).

The resulting unique earlier emergence of the action potential seen in the PV interneurons in response to simultaneous stimulation induces a faster feedforward inhibitory response in principal neurons. This inhibition creates only a short temporal window in which excitatory input from the AiP and LA can coincide to result in enhancement of the EPSP. This effect could be beneficial for synchronizing activity along the PER-LEC axis when the LA is active (Pouille & Scanziani, 2001). This fast feedforward inhibition, which is homogeneously recruited by a population of interneurons, can set the threshold for firing in principal neurons and therefore select only small neuronal populations to be involved in the neuronal processing (Shadlen & Newsome, 1998). The mechanism for attenuation of the spike timing, by interaction of synaptic input in PV interneurons, is proposed to be relevant for the coordination of neuronal firing across brain areas. During memory consolidation, the temporal coordination of hippocampal and cortical firing is not precise, likely due to the regulation and segregation of spike trafficking by intermediate structures such as the perirhinal and entorhinal cortex (Pennartz et al., 2002).

The feature of the amygdala to interact with activity in the rhinal cortex neurons is not specific to the PER-LEC network. The basolateral amygdala (BLA) is for example also involved in regulation of medial entorhinal cortex activity when spatial or contextual learning is modulated by emotion (Wahlstrom et al., 2018). Wahlstrom and colleagues (2018) showed that memory performance is specifically enhanced when the BLA input to the MEC is active

in the 8 Hz theta. Since the inhibitory neurons in the MEC play a crucial role in the spatial information processing (Couey et al., 2013), it is possible that BLA activity interacts with the interneurons to modulate spatial information processing. However, whether principal neurons and interneurons in the local MEC network play a comparable role in the modulation of MEC activity by the BLA remains to be revealed.

## Future directions

In this dissertation, we provide a mechanism for the regulation of activity transmission through the PER-LEC network. Although the insight in how synaptic input from the neocortex as well as the amygdala is processed by the PER-LEC is obtained in a horizontal slice preparation, the specific role of the various projecting fibers is not yet clear. It is possible that specific projections target specific groups of neurons to influence to tight excitatory-inhibitory balance and therefor favor transmission of activity. Such a projection is for example found in the form of cholinergic inputs from the basal forebrain, which regulate inhibitory activity in the EC as well as in the auditory cortex (Apergis-Schoute, Pinto, & Paré, 2007; Kuchibhotla et al., 2016). Targeting specific groups of neurons from areas which project to the PER-LEC network with light-activated channelrhodopsins and recording how PER-LEC neurons combine these inputs to firing patterns could provide a more detailed insight in the integrative properties of the neurons in the PER-LEC network. Furthermore, the rules for selectivity of the rhinal gate could be studied in more depth by these specifically targeted projections.

Additionally, it has been shown that long range GABAergic projections onto interneurons in the LEC can regulate the activity of the EC interneurons and principal neurons (Fuchs et al., 2016; Melzer et al., 2012). Although long range GABAergic projections from the LA to the PER-LEC network are not found in the experimental paradigm used in this dissertation (chapter 5), *in vivo* anatomical data confirmed a GABAergic projection from the basolateral amygdala towards the entorhinal network (McDonald & Zaric, 2015). These long range projections are likely involved in synchronizing oscillatory activity between the amygdala and the EC, the functional implications and the involvement in the emotional enhancement of memory however, remain to be revealed.

A second relevant question for the role of the amygdala in the modulation of cortical input in the PER-LEC network is: how are the amygdalar and neocortical inputs organized on the dendritic tree of the local circuit neurons? As shown in box 3, the localization of synapses is essential for the transmission of synaptic input to the soma. If synaptic inputs from different brain areas project onto the same compartment of the dendritic tree, the chance that they coincide and facilitate each other are much larger than in case they project onto different branches. Furthermore, a hierarchy in which information is most determinative for the output of the neuron depends on the proximity, size and weight of the synaptic contacts onto the dendritic tree (Stuart & Spruston, 2015). Anatomical studies together with single cell dendritic patching or voltage sensitive dye imaging could reveal the dendritic depolarization of PER-LEC neurons by AiP and LA input, to answer the fundamental questions of localization and hierarchy of synaptic input from the AiP and LA.

## Conclusive remarks

This dissertation was written based on the experiments investigating the fundamental question how the PER-LEC network can gate neuronal activity and how this gate can be modulated by the lateral amygdala. We propose that the superficial layers transmit neuronal activity from the cortex towards the hippocampus while the deep layers are inhibited. Furthermore, lateral amygdala activity can influence the activity evoked by neocortical synaptic input, mainly via the temporal regulation of the firing of local PER-LEC PV interneurons.