Walk of life

How brain state, spatial, and social context affect neural processing in rat perirhinal cortex, hippocampus, and sensory cortices

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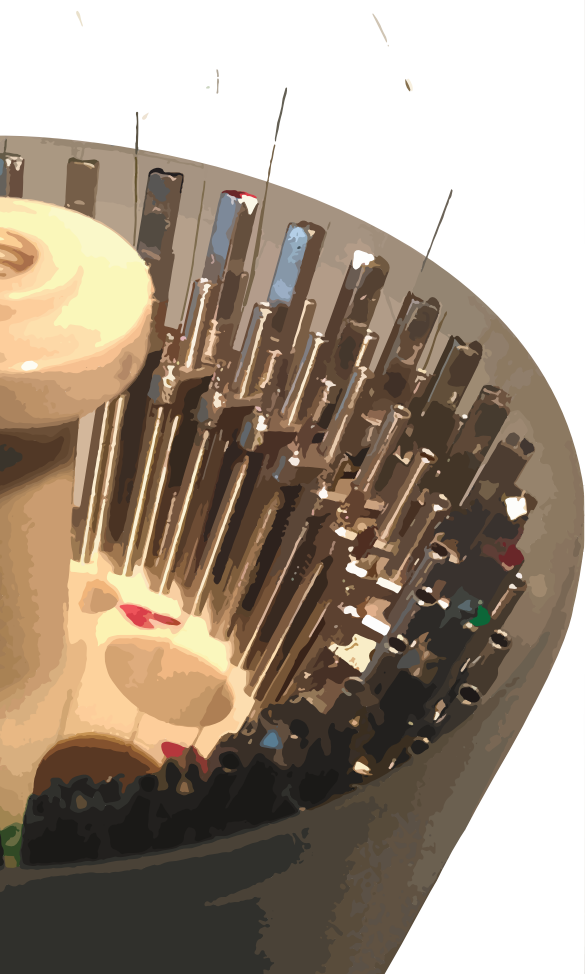
Chapter 6

Discussion



Preface

The previous experimental chapters contain data from two experiments; Touch and See (chapters 2-4) and Rat Robot (chapter 5), see Figure 1 of the introduction. The different chapters, however, pertain to very different research questions. This diversity makes it difficult to have a clear singular story to interpret the results. Because I do not believe it is proper to force the above results in a single mould I will take a slightly different approach and write a separate discussion for each chapter. Writing four full-fledged discussions is too much and writing four small discussions does not feel very satisfying. As such I have decided to write a more expansive discussion about chapter 4, the unexpected perirhinal results, while including small discussions about the remaining chapters in the end. I have chosen to expand on chapter 4 because I have had the lead in those analyses and I am most fascinated by those unexpected results. Before we start with interpretations, first a summary of the results.

Overview of the chapters

In chapter 2 we first looked into the state and cell type dependent dynamics of phase synchronization of extracellularly recorded signals within S1BF (primary somatosensory cortex, barrel field). After focussing on local dynamics, we broadened the scope and looked at long range interactions between the four different brain areas which we recorded. Finally, we compare our extracellularly recorded data with intra-cellular recordings made by Luc Gentet (Gentet et al., 2010).

First, we confirmed the existence of gamma in S1BF during naturalistic behaviours. In addition to gamma we found prominent entrainment of S1BF spikes to beta rhythms. Interestingly, while gamma locking was associated with increases in firing rate, stronger beta locking was correlated with lower firing. For both fast-spiking putative inhibitory and excitatory neurons beta phase locking was highest during the baseline period (inter trial interval), while gamma phase locking increased during locomotion. Excitatory neurons which fire action potentials with short inter-spike intervals (ISI) were more strongly locked to both beta and gamma than the neurons with longer ISIs were. Within the short ISI group, excitatory neurons which had more irregularly bursting firing patterns were more strongly locked to beta.

To investigate the mechanisms by which beta and gamma oscillations could be generated, we explored the temporal order at which the different sub-populations of neurons fired with respect to the oscillations. Both putative inhibitory and excitatory neurons fired at the same time during the cycle (around the trough). However, we observed a bimodal distribution in the phase locking to gamma in the group of putative interneurons. An early group fired before the excitatory neurons, while the late group fired after. The early group shows consistently higher phase-locking to gamma than the late group and is not modulated by different behavioural states. In contrast the late firing group of putative interneurons, similar to excitatory cells, increase their gamma locking during locomotion. This

would suggest that the gamma oscillations could be generated in a three-step process by combining elements of the ING and PING models.

After looking at local beta and gamma in S1BF we expanded our field of view to include the other areas; CA1 of the hippocampus (HPC), perirhinal cortex (PRH), and monocular primary visual cortex (V1M). All areas showed within-area gamma phase locking, which was increased by locomotion. Despite the presence of local gamma in each area, we did not observe any notable inter-areal spike phase locking to gamma. The same held true for LFP-LFP (local field potential) locking within and between areas. Looking at lower frequencies, during the locomotion period, we did find inter-areal locking between S1BF neurons and CA1 LFPs in the beta range and S1BF neurons with PRH and V1M LFPs in the delta range. Both V1M and PRH neurons lock to CA1 LFP, during locomotion, in the beta and beta/theta range, respectively. CA1 neurons phase locked in the theta range to LFPs from all other areas. Given the robustness of hippocampal theta and the strong inter-areal LFP-LFP phase locking in the theta range, this could be the result of volume conduction.

Splitting the intracellular dataset based on the same waveform characteristics used for the extracellular dataset we show that the group of neurons we defined as putative interneurons in the extracellular dataset contains two different sub-groups of interneurons, parvalbumine positive (PV+) and somatostatin positive (SSt+) cells. PV+ cells display strong mutual inhibition and gap junctions. In addition, optogenetic activation of PV+ has been shown to induce gamma oscillations (Bartos et al., 2007; Cardin et al., 2009; Buzsáki and Wang, 2012). These properties fit with the early spiking interneuron group. SSt+ cells on the other hand do not receive many inhibitory inputs from PV+ cells. As late firing neurons, they could inherit their gamma rhythm from the excitatory population.

Similar to the extracellular data, the intracellular data revealed that both inhibitory and excitatory neurons showed increased gamma locking in their membrane potentials during active states, relative to baseline. This is not trivial, because gamma is not regularly found in intracellularly recorded membrane potentials (Poulet and Petersen, 2008).

In chapter 3 we investigated changes in neuronal functional connectivity across different brain and behavioural states. Looking into single unit activity binned across 600-900ms bins we did not aim to capture the precise information being communicated. Instead these larger bins assess, how global firing rate in- and decreases of unit A are correlated to firing rate modulations of unit B. Information transfer was measured using two non-linear measures for functional connectivity, conditional mutual information (cMI) and conditional delayed auto-mutual information (cDAMI), during three different brain states; active wakefulness (AW), quiet wakefulness (QW), and non-REM sleep (NREM). cMI measures the co-modulation between pairs of neurons. cDAMI indicates recurrent activity or, in other words, to what extent the future activity of a neuron can be predicted by its current activity.

Both cMI and cDAMI were state-dependent and higher during AW and QW compared to NREM. Within an area, cMI was generally highest during QW, with the exception of the primary sensory cortices, where there was no difference between AW and QW. Between areas cMI was highest between pairs of neocortical neurons, while hippocampal-neocortical interactions were most pronounced during AW. For cDAMI there appears to be a split between neocortex and allocortex. In the neocortex, cDAMI was lower during NREM as compared to AW and QW. In hippocampus, cDAMI was highest in AW, followed by QW and lowest in NREM.

Next, we divided our dataset into pairs of putative excitatory or pairs of putative inhibitory neurons. Functional coupling within an area was not modulated by behavioural state. Connectivity between areas was nearly constant for inhibitory pairs but reduced from AW to QW to NREM in excitatory pairs. Inter-areal connectivity between excitatory neurons was largely state-dependent, while intra-areal connectivity was not. Alternatively, interactions between interneurons, both intra- and inter-area, were stable across behavioural states.

Finally, we distinguished between neurons which showed modulation by the task and neurons which did not. Task modulated neurons formed a distinct network during AW, displaying increased cMI. These task modulated neurons remained more coupled to other task modulated neurons during QW and NREM, compared to pairs of task modulated and task non-modulated neurons. Interestingly, pairs of non-task modulated neurons also displayed higher functional connectivity compared to mixed pairs during QW and NREM. This indicates a split of two sub-populations of neurons which remained segregated even outside of the task.

In chapter 4 we describe a possible new coding function of the perirhinal cortex. We report PRH neurons which display selective activity for large segments of the task environment. These neurons show sustained activations or deactivations which are coupled to an entire arm of the figure-8 maze, left versus right, versus middle segment. Interestingly, single neurons could show a sustained increase in firing rate on one arm (e.g. left arm) and a sustained decrease in activity on the other arm (e.g. right arm). This bimodal differentiation hints at a clear task for environmentally driven differentiation between large maze segments.

The spatial extent of PRH activations was much larger than the dorsal CA1 place fields which were simultaneously recorded. In addition, unlike HPC place fields, which are scattered throughout the environment, the sustained activations of PRH were locked to the branching points of the set-up. The sustained PRH activations could not be explained by other task variables, like correct versus incorrect trials, the locations of the visual cues, somatosensory inputs, or by short-term memory effects. Left versus right sided trials appeared to be the important discriminant, irrespective of what happened within those trials.

To assess whether these responses could be facilitated by top-down hippocampal input we looked at phase locking of PRH spikes to HPC LFP. We found selective locking of PRH spiking activity to HPC theta. The strength of this

phase-locking was correlated with the left/right selectivity of the PRH neurons. The more selective the PRH neuron, the more strongly it locked to HPC theta.

In the final chapter (chapter 5) we studied whether the hippocampus codes positions of others as well the position of the self. In this chapter, we investigated if and how a rat can use place fields in the hippocampus to not only keep track of where it is, but also where another moving agent is in space. We did not observe any mirror-neuron like properties in CA1 of the hippocampus. Place fields found when the rat was in a particular area did not "reactivate" when seeing a robot move through that same space. Instead, we did observe robot-associated place field modulations for cells firing in response to the current task phase or location of the rat. Robot induced place field modulation occurred both between different tasks, i.e. front versus mid task and within tasks, i.e. during the outward and inward trajectories of the robot.

Neural activity for the animal's position and task-induced stereotyped positioning of the animal are interwoven. Because of this it is important to control for rat movement while investigating place-modulated firing caused by the trajectory of the robot. We utilized mutual information measures similar to those used in chapter 3, to investigate the linear and non-linear correlation between neural activity and the position of the robot. Using rat position as different 'conditions' we applied conditional mutual information to correct for the movements of the rat. We observed a significant number of cells whose firing rates correlated with robot position even when we controlled for the position of the rat. These results provide strong evidence that CA1 activity is not only modulated by the position of the self, but also by movements of another agent. This modulation is present in both excitatory and inhibitory neurons.

Recording techniques – Quad drive

As can be seen in the result summaries above, the experimental chapters in this thesis cover several different topics and different types of analyses. Naturally the results and the analytical methods will draw most attention. However, I would first like to focus on the step preceding the results, on the recordings. A large part of my PhD project consisted of developing a new recording device, dubbed the 'quad drive', see Figure 1 of the introduction. The quad drive was designed in collaboration with the technology centre of the University of Amsterdam. It is an expansion of the classic 14 tetrode hyperdrive from the McNaughton and Barnes lab (Wilson and McNaughton, 1993; Gothard et al., 1996; Lansink et al., 2007). In the new drive, we increased the number of tetrodes from 14 to 36. This more than two-fold increase allowed us to split our recording tetrodes into several bundles, with each bundle aimed at a different target region. This way the quad drive allowed us to record four different brain areas with 9 tetrodes directed to each area. These multi-area recordings yielded a unique dataset which forms the basis of chapters 2-4. Using a new drive, however, also came with a new set of challenges.

The quad drive required an update of all hardware used; new connectors, commutator and recording device (Digital Lynx, Neuralynx).

There were two main recurring difficulties when working with the quad drive, which will need to be taken into account in all future projects. The first is tetrode placement and the second is scale.

Our four target areas necessitated four craniotomies. In order to maintain stability of the skull and to reduce the chance of infections, we opted for four small craniotomies versus resecting half of the parietal plate. One hole for each bundle aimed at one of the four different target areas. During surgery, however, the brain exhibits some swelling, which complicates drilling craniotomies adjacent to previous craniotomies. Final placement of the quad drive is often a tight squeeze. Four targets also add another complication. The surface of the brain is rounded and as such bundles holding tetrodes which are aimed at more lateral targets should to be longer than medial ones in order for all bundles to touch the brain at the same time.

These two difficulties are the likely cause of the fact that we were unable to make high-yield visual cortex recordings. V1M was the only target area located directly underneath a craniotomy. For the other recorded areas, the tetrodes either travelled a long distance or were inserted at an angle such that the final recording sites were away from the craniotomy. The latter would likely be the best way to improve yield of visual cortex recordings. Given the shallow location of V1 this would require tetrodes to be inserted at a very wide angle with respect to the skull. This is doable, but a wide angle of one bundle places constraints on positioning of the other bundles.

The second recurring problem - that of scale - could be considered a self-inflicted luxury problem. However, that does not make it less real. Double the number of tetrodes means double the amount of time. The influence of scale is most notable during gold-plating of the tetrode tips to reduce impedance, turning the tetrodes to their target locations, making lesions at the end of recordings for later validation of recording sites and during data analysis.

For gold-plating and lesions the solution was to automate. The nanoZ (Neuralynx) can be used for measuring the impedance of tetrodes and allows the controlled application of currents to each separate electrode of the tetrodes for gold plating. Adding gold to the tips of the electrodes reduces their impedance, which allows us to detect smaller electrical signals in the brain. The nanoZ is unfortunately not 100% dependable, so a manual back-up was always required. Nonetheless, using the nanoZ greatly reduced the gold plating time from 3,5 to 2 hours.

In both the ‘old’ and the ‘new’ drive all tetrodes are individually movable, which allows very precise placement in their target regions. With the 14-tetrode drives, it was not uncommon to take 1-3 hours per day to position the tetrodes, especially during the first week following surgery. This first week after surgery is, however, also the recovery period for the animal. Turning tetrodes for 2-6 hours

each day will induce mechanical stress on the drive and physical stress to the animal. When the rat was properly habituated, turning hardly stressed the animal during the first ~2 hours. After this initial period the animals became gradually more and more agitated. This agitation and the associated movement decreased turning precision and necessitated more restraining of the animal. As such, it is my opinion that shorter turning sessions, especially during the initial days following surgery, will improve longevity of the implant. Turning faster requires more preparation and experience to work properly. Here it is very important to be mindful of the different patterns of brain activity (markers for anatomical locations) one encounters while turning the tetrodes. This is also where recording multiple brain areas can be beneficial. More areas yield more different markers. For instance, one clear marker when approaching the pyramidal layer of CA1 is the emergence of ripples in the LFP. If we encounter ripples earlier than anticipated this could indicate that the tetrodes were implanted a little deeper than intended, or that the recorded brain was a little flatter than anticipated by looking at the brain atlas (Paxinos and Watson, 2007). Additionally, keeping track of which perirhinal tetrodes move through the deeper layers of the cortex (granular, layer IV, or sub-granular layers, layer V-VI) and of which move through the corpus callosum, can give an indication about how lateral the tetrodes were with respect to the atlas. Information about the small deviations in anterior-posterior and medio-lateral positioning can be used to position tetrodes in all target areas.

Design choices

Performing multi-area tetrode recordings in freely moving animals is a complicated yet powerful technique. Having both single unit and LFP data while the animal exhibits different behaviours makes the dataset very diverse. Every method we currently have to record electrophysiological activity in the brain is a trade-off.

Recording from freely moving animals leads to more naturalistic behaviours, compared to recording head fixed animals. However, using freely moving animals we lose experimental control relative to head fixed recordings. This has an impact on the work presented in chapter 2. With the current set-up, it is impossible to investigate dynamics of neural signals with respect to precise individual whisker movements. The top view from the overhead camera was too broad to determine whisker movements. The initial set-up incorporated a high-speed camera to measure whisking activity. Changes in the task, relative to the first set-up and the second version of the set-up omitted a fixed whisking location. As such we had to let go of precise whisker tracking with the high-speed camera. Making use of a head mounted camera could help overcome this issue, however doing that was not practically feasible to add to the Touch and See experiment.

Despite the visual nature of the task (two-choice visual discrimination), visual responses are no major parts of chapters 2-4. This is in large part due to the above-mentioned difficulties in obtaining high-yield visual cortex recordings. A second reason could be that the continuous movement of the animal prohibits

stable representations of the stimuli. To allow for a more stable input, head and body movement of the animal would have had to be restricted. Head fixing animals would have been one of the solutions, even though this precludes natural interaction with the environment. Since head fixation was not compatible with our experiment we tried to minimize some of the variability by using relatively narrow walkways. This did not limit head movements, but it did stabilize body position. Given the spatial nature of our task, limiting variation in body location helps regularizing the behaviour.

In chapters 2,3 and 5, spikes from recorded neurons were clustered into groups based on waveform properties. Looking at spike waveform and firing properties, it is possible to separate extracellularly recorded neurons into pyramidal cells and interneurons (Csicsvari et al., 1999; Barthó et al., 2004; Mitchell et al., 2007). Most interneurons have high firing rates and short waveforms (peak-to-trough interval) with typically more convex repolarizations, with respect to pyramidal cells (see Figures 3 and 10 of chapter 2, Figure 6 of chapter 3, and Figure 6 of chapter 5).

Making this rough split is very informative and being able to distinguish between excitatory and inhibitory neurons adds an extra dimension to analyses. For a more precise segmentation between pyramidal cells and different types of interneurons, however, other techniques like optogenetics and histological identification are required (Klausberger et al., 2003; Tukker et al., 2007; Cardin et al., 2009; Gentet, 2012). Combining techniques can increase our knowledge to better define the identity of extracellularly recorded neurons (Matthews and Lee, 1991; Harris et al., 2000; Henze et al., 2000). An example of this is shown in chapter 2.

Oscillations in the rat barrel cortex

In chapter 2 we investigated the roles of oscillatory activity in information processing, both within and between brain areas. We show that gamma oscillations (30-90 Hz) occur in the barrel cortex during naturalistic behaviours. Gamma oscillations were most prominent during locomotion. This fits with the current literature which generally associates gamma with active processing (Buzsáki and Wang, 2012; Bosman et al., 2014; Vinck and Bosman, 2016).

There is an ongoing debate about how gamma rhythms are generated. There are two competing models which can explain gamma oscillations: the ING (interneuron network gamma) and the PING (pyramidal interneuron gamma network). In the ING model network gamma is generated by cyclic mutual inhibition between interneurons. In this model, asynchronous excitatory inputs are enough to engage inhibitory activity which can generate a gamma rhythm (Whittington et al., 1995; Bartos et al., 2007). As long as there is enough network input, the cyclic inhibition will self-organize to oscillate at gamma frequencies. In PING networks the activity of interneurons is driven by pyramidal neurons (Wilson and Cowan, 1972; Csicsvari et al., 2003). In these models, excitatory activity precedes the inhibitory activity. Concerted excitatory activity will activate inhibitory inter-

neurons. This excitation will induce a wave of inhibitory rebound. This inhibitory wave decreases firing of excitatory neurons. The reduced excitatory activity in turn leads to decreased inhibitory activity which allows the excitatory neurons to become active again.

One difference between ING and PING type models is that ING type gamma can arise following asynchronous excitatory activations, while PING relies on synchronized excitatory firing. This difference between ING and PING networks could dictate the order in which neurons fire. In ING networks interneurons drive rhythmic excitatory firing, while in PING networks strong excitatory activity precedes inhibitory activation (Whittington et al., 2000; Tiesinga and Sejnowski, 2009; Buzsáki and Wang, 2012). The current literature is divided, describing both delays and advances of inhibitory neurons with respect to excitatory neurons within gamma cycles (Bragin et al., 1995; Csicsvari et al., 2003; Tukker et al., 2007; Hájos and Paulsen, 2009). In our experiment, we initially found no gamma phase delays or advances of inhibitory neuron spiking with respect to excitatory neurons. Looking more closely at spike timing, our results (Figure 6C of chapter 2) showed a bimodal distribution of gamma phase angles for interneurons. The "early" group fired roughly 1,5-2 ms before the excitatory neurons, while the "late" group followed about 3 ms after the excitatory neurons. Interestingly, this bimodality was specific for gamma. No such distinction was found for phase locking to beta (Figure 6D of chapter 2). This raises the question: Are the early and late locking interneurons two different subtypes of interneurons?

When segmenting the waveforms from the targeted intracellular data by using the same criteria we used for the extracellular dataset, we found that what we defined as putative inhibitory neurons consisted of at least two different types of interneurons; parvalbumin positive (PV+) and somatostatin positive (SSt+) neurons. It is remarkable how well the intracellular and extracellular waveform segmentations overlap, see Figures 3 and 10 of chapter 2. This provides insight in how we can use knowledge obtained by targeted intracellular recordings in segmenting extracellular neural data. The literature highlights the importance of PV+ in gamma. Cardin et al. (2009) showed that optogenetic activation of PV+ neurons in rat barrel cortex in vivo induced gamma oscillations. Light stimulation at different frequencies did not universally induce oscillatory activity at that same frequency. Instead, PV+ interneurons specifically oscillated in the gamma range (20-80Hz), while stimulating excitatory pyramidal neurons induced oscillations at lower frequencies (8-24Hz theta/beta range). Sohal et al. (2009) reported induction of gamma by optogenetically stimulating PV+ neurons in vitro in the mouse prefrontal cortex. Stimulating and inhibiting PV+ neurons enhanced or suppressed gamma oscillations, respectively. In addition, non-rhythmic excitatory inputs resulted in PV+ mediated feedback inhibition which enhanced gamma power in the LFP.

PV+ expressing basket cells display various properties which make them especially suited to assist in the generation of gamma oscillations. Basket cells provide perisomatic inhibition which is hypothesised to be important for the induction of gamma oscillations. Basket cells are highly interconnected, also via gap

junctions (Bartos et al., 2007), and as described above have been shown to have an inherent resonance at gamma frequencies.

Whereas PV+ cells are often associated with gamma oscillations, SSt+ cells are not (Tukker et al., 2007; Buzsáki and Wang, 2012). SSt+ expressing Martinotti cells mainly target distal dendrites, have few connections to other Martinotti cells, receive few inputs from PV+ neurons and show an inherent rhythmicity closer to the theta range.

In our data, the early gamma phase locked group of interneurons showed stronger locking to gamma oscillations than the late group. However, they did not show modulation by behaviour, while the late group displayed increased gamma phase locking during locomotion. The early phase locked group could correspond to PV+ cells. The response pattern of early phase locking neurons fits with the above described function of PV+ neurons and results from Perrenoud et al. (2016), who reported strong, but not condition dependent, gamma phase locking for PV+ cells.

The early group of fast spiking neurons (FS) could entrain gamma in pyramidal neurons and the pyramidal neurons in turn could drive gamma phase locking of the late group of fast spiking neurons. Both pyramidal cells and the late group of FS cells show modulation of gamma phase locking by behaviour. Both groups show increased gamma phase locking during the active movement phase, which was also associated with increased firing rates and increased gamma power in the LFP. This would fit with properties of SSt+ Martinotti cells which receive mainly excitatory inputs (Gentet, 2012; Gentet et al., 2012) and do not show strong inherent gamma rhythmicity. These results suggest that ING and PING models could co-exist to generate gamma oscillations.

Unfortunately, we could not directly validate this hypothesis, because we could not determine the phase angles of the intracellularly recorded action potentials. The large fluctuations in membrane potential caused by action potentials distort analysis of phase. As such action potentials had to be removed in order to measure oscillatory activity. In order to test the hypothesis that the early FS cells are made up of PV+ neurons while the late group corresponds to SSt+ neurons, future intracellular experiments should include a separate electrode to record extracellular LFP. This separate LFP trace will allow phase angles to be determined without pollution by action potentials.

Despite finding gamma in all recorded areas, we did not observe significant inter-areal coupling in the gamma range, even during the most “gamma heavy” period; the movement phase. The fast and very transient nature of gamma does not make it especially suited for long range communication. Gamma oscillations carry relatively little energy and conduction delays could easily mess up the precise time required for gamma coupling. There are however studies which have described gamma coupling across long range connections in the cortex (Engel et al., 1991; Buschman and Miller, 2007; Gregoriou et al., 2009; van Kerkoerle et al., 2014; Bastos et al., 2015). Long range interneurons could facilitate this long-

range gamma coupling. These neurons have been found to have very thick axons. These thick axons allow increased conduction speed. Through these thick axons inter-hemispheric gamma phase coupling can be achieved (Buzsáki et al., 2004; Jinno et al., 2007).

Bouts of gamma oscillations are often found to locked to slower oscillations like theta (Bragin et al., 1995; Sirota et al., 2008). This is called cross frequency coupling. Here bouts of gamma are locked to a specific phase of the slower oscillation. Slower oscillations have more energy and the wider waveforms are less affected by jitter in timing due to conductance delays of signals travelling over longer distances between areas. As such slower oscillations are more robust for use in long range communication. Indeed, we find inter-areal spike-LFP and LFP-LFP locking in the beta and theta range. This phase locking is increased during locomotion, especially to CA1 LFP, but also to LFPs recorded from the other areas; S1BF, PRH, and V1M. When zooming in on the barrel cortex, we found no differences in phase preference between any of our S1BF cell types and CA1 LFP to low beta/high theta oscillations (14 Hz, see Figure 8 of chapter 2). This lack of cell type specificity is interesting when contrasted with the strong differences we have observed between the different cell types in local gamma phase locking.

Due to the highly developed organization of the hippocampus, CA1 is able to generate a very strong theta rhythm. As such we have to make sure that theta rhythms measured in the LFP of other brain areas are not volume conducted from the hippocampus (Sirota et al., 2008). Because of the changes in inputs, curvature, and orientation of the hippocampus there is not just a single theta rhythm. Instead the phases of the theta oscillations shift across hippocampal layers and medio-lateral position within CA1 (Buzsáki, 2002; Lubenov and Siapas, 2009). These multiple oscillations with different phases are all volume conducted. Even though the PPC and WPLI are designed to be less sensitive to volume conduction, they work best against noise from single sources. Indeed, our results suggest that the theta oscillations found in S1BF, PRH, and V1M are likely volume conducted signals from CA1. CA1 neurons phase locked more strongly to LFP from the other three areas, than neurons from the other areas locked to CA1 LFP. In addition, we did not observe theta phase locking in spike-LFP pairs within areas other than CA1. Finally, CA1 neurons locked better to LFP signals recorded from areas which are closer to the hippocampus, than LFPs from areas which lie further away.

In areas other than CA1, there could be a locally generated theta rhythm on top of the volume conducted signals from CA1. In our data, this is unlikely because of the lack of within-area phase locking to theta rhythms.

The theta/beta and gamma oscillations we found both increased during the locomotion phase of the task. The theta/beta component likely has a hippocampal origin, while the gamma rhythm is hypothesised to be more locally generated. Cross-frequency coupling could be a mechanism to time gamma bouts to facilitate both short- and long-range communication. However, we did not test this yet in our data. Future analysis could focus on relative timing of inter-areal gamma bouts.

The results in Chapter 3 underscore the importance of classifying recorded neurons. Looking into functions of different sub-classes of inhibitory, but also excitatory neurons could yield important insights into functioning of neuronal assemblies and cortical columns. Classification of extracellularly recorded neurons is complicated. Waveform shape can change depending on recording location with respect to dendrites or the soma. Furthermore, at this point there is a lack of knowledge of how cells can be classified beyond distinguishing broad spiking putative pyramidal and fast spiking putative interneurons. Combined intra- and extracellular recordings from defined neural populations could assist in defining waveform and firing characteristics for distinct cell classes. This is initially a high-effort, low-reward job, but more information of how to classify and interpret extracellular recordings would be most instructive. Especially with the rise in popularity of extracellular recordings and the increased prevalence of commercial probes with more and more recording channels this type of information could be invaluable.

Functional connectivity within and between areas and across different behavioural states

In chapter 3 we investigated inter and intra-areal information transfer. We show that different types of neurons recorded in 4 different brain areas (S1BF, V1M, PRH and HPC) display differential functional connectivity across different brain states. NREM sleep, but not active or quiet wakefulness, has been associated with decreased functional connectivity between brain areas. We show that even though inter-areal functional connectivity is decreased, within-area connectivity is maintained. We have found that the decrease in inter-areal coherence during NREM sleep correlates with a decreased proportion of inter-areally coupled excitatory neurons. No such change was observed in intra-areal coupling or coupling between interneurons. Finally, we observed that task modulated neurons and non-task modulated neurons form separate functional networks. Pairs of either task-modulated or non-task modulated neurons showed an elevated proportion of significant correlations with respect to mixed pairs during quiet wakefulness and non-REM sleep. Strikingly, task-modulated neurons show decreased conditional delayed auto-mutual information (cDAMI) with respect to non-task modulated neurons. Thus, it is more difficult to predict the future firing rate for task modulated neurons when their current firing rates are known, than for non-task modulated neurons. This seems counterintuitive when thinking about reactivation.

Reactivation occurs both within and between areas (see introduction; Lee and Wilson, 2002; Ji and Wilson, 2007; Lansink et al., 2009). Throughout a trial or task phase excitatory neurons usually fire in specific sequences. Using the example of hippocampal place cells, place cells are activated in a specific sequence when the animal traverses the environment. During a pause in the trial (usually after reward) or post-task sleep, these same sequences are reactivated during

ripples. Ripples are high frequency oscillatory events (100-300 Hz) in the hippocampus. During ripples these previously encountered sequences are replayed in a time compressed manner.

One would expect firing sequences of task modulated neurons to be preferentially reactivated compared to sequences of non-task modulated neurons, since the latter ones do not carry task-relevant information (or at least as far as we can surmise). As such one would expect increased cDAMI scores for task modulated neurons, especially during non-REM sleep (NREM). The opposite was the case. This is probably due to a difference in time scale. The mutual information measures used 600-900 ms time bins. This time scale is significantly longer than the duration of an average ripple duration of about 100 ms. This could explain the difference we observed. If we assume that task modulated neurons are preferentially recruited for reactivation, the fast dynamics of ripples and time compressed replay can selectively reduce the recurrent activity as measured with cDAMI for this subgroup of neurons. To test this, mutual information should be measured on shorter time scales. We did calculate cMI at short timescales (2-50 ms), but these results did not show a clear relationship between cMI and the cross-correlograms of pairs of neurons. Because of this, these results were excluded from the paper.

In a follow up analysis, conducted by Umberto Olcese (Olcese et al., under review), transfer entropy (TE; Schreiber, 2000) was used to calculate a non-linear version of Granger causality (Barnett et al., 2009). This measure calculates how the current firing rate of a neuron influences the firing rate of another neuron in the future. As such this measure bears some similarity to cDAMI, which investigates how the current firing of a neuron will influence its own future activity. Using this measure, information transfer could be calculated on short time-scales (STE, 2-10 ms) as well as long time-scales (LTE, 600-900 ms). We indeed found that ripples are important for inter-areal short time-scale information transfer. During NREM sleep STE decreased significantly when ripple periods were excluded. Interestingly this decrease was specifically observed in pairs of PRH and HPC neurons, see Figure 1A-B. No effect of ripples was found in LTE for any of the comparisons. These results indicate the importance of ripples for long range communication at short time scales during sleep, especially between HPC and PRH. Hippocampal-cortical interactions during sleep are an important prediction from the two-stage model for memory consolidation (see Figure 3B of the introduction).

During quiet wakefulness and NREM sleep, inter-areal STE was increased in task modulated versus non-task modulated pairs of cortical and hippocampal neurons, see Figure 1C. This could be in line with consolidation of task modulated information.

We also found increased LTE in non-task modulated pairs of neurons from distinct cortical areas, see Figure 1D. At this point it is unclear what the role could be of this increased information transfer between non-task modulated neurons during NREM sleep.

Both in chapter 3 and our follow up analyses there seems to be a clear distinction between task modulated and non-task modulated neurons. These neurons

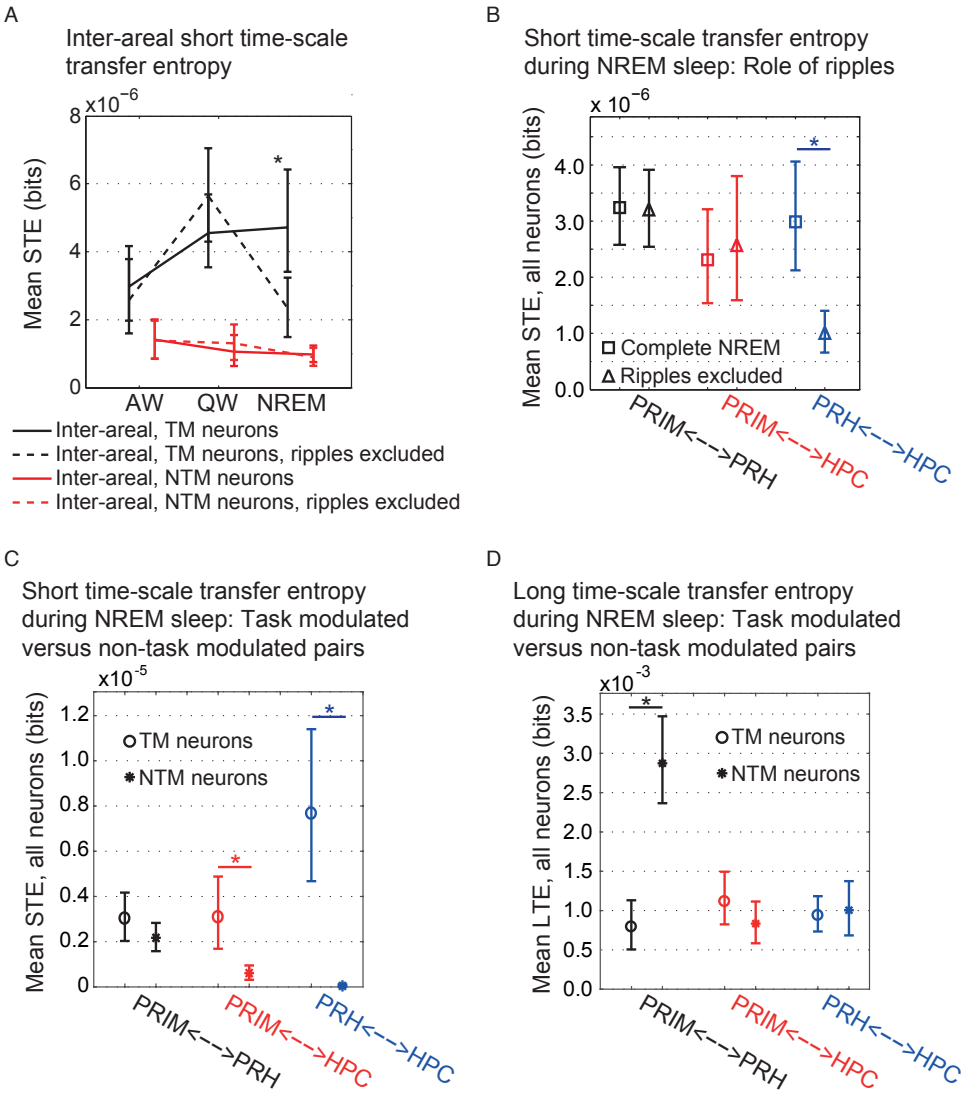


Figure 1 | Short and long time-scale transfer entropy. A) Overview of average inter-areal short time-scale transfer entropy (STE) during different behavioural states. The behavioural states are active wakefulness (AW), quiet wakefulness (QW), and non-REM sleep (NREM). In black STE is shown between pairs of task modulated (TM) neurons Analyses were performed on the same sessions of the Touch & See dataset as used in chapter 3. Pairs of non-task modulated (NTM) neurons are drawn in red. Dashed lines indicate STE when ripple epochs are excluded. B) STE during NREM sleep between different areas, both including and excluding ripple epochs. S1BF and V1M neurons are combined into primary sensory cortex (PRIM). Pairs consisting of a PRIM and a PRH neuron are shown in black, pairs of PRIM and HPC neurons are shown in red, and pairs of PRH and HPC neurons are displayed in blue. Squares indicate STE during the whole NREM period. For the triangles all ripple epochs were excluded. C) STE between pairs of TM and NTM neurons in different areas. Colour coding is the same as in (B). Open circles indicate pairs of TM neurons, asterisks show pairs of NTM. D) Same is (C), but for long time scale

transfer entropy (LTE). Error bars indicate bootstrapped confidence intervals. * indicates a significant difference, bootstrap test, α = 0.05. Images were adapted from Olcese et al. (under revision).

may form two different functional networks which not only behave differently in the task environment, but also during sleep. In our experiments the animals were highly trained in the task, so task modulated neurons have been co-activating for months, which may have strengthened their interactions. It would be interesting to investigate cMI, cDAMI, STE, and LTE while animals learn the task. This way we may observe a segregation in function of task and non-task modulated neurons.

Perirhinal cortex

Unexpected findings

The results described in chapter 4 were unexpected. We did not anticipate to find sustained responses which segmented the task environment. We aimed to find sensory responses correlated with different parts of the task, which included a visually guided choice and texture patches indicating reward size. We indeed found single unit responses to all these different sensory events in the task. In addition, however, we found firing patterns which matched the spatial layout of the figure-8 maze. As such I would like to take the opportunity to zoom in on the perirhinal cortex and its associated function and discuss how our results, although unexpected, could fit with our current understanding of perirhinal cortex (PRH) functioning.

The perirhinal cortex PRH is situated on the border between sensory association cortex and the hippocampal formation, see Figure 2A. Here it serves an important function as a transition area between the sensory neocortex and the medial temporal lobe, which is associated with memory. On the one hand the PRH is a polymodal association area, receiving inputs from many uni- and polysensory areas (see Figure 2B; Burwell et al., 1995; Burwell and Amaral, 1998; Burwell, 2001; Suzuki and Amaral, 1994; Furtak et al., 2007b). On the other, the PRH is an input and output hub of the medial temporal lobe (MTL), exerting an important function in recognition memory (see Figure 2B; Burwell et al., 1995; Burwell and Amaral, 1998; Insausti et al., 1997; Witter et al., 2000).

As described in the introduction, two major cortico-hippocampal pathways have been defined (Goodale and Milner, 1992; Burwell, 2000; Witter et al., 2000; Furtak et al., 2007b). One pathway, associated with coding for objects ('what' pathway) goes from PRH via the lateral entorhinal cortex (LEC) to the HPC. The second pathway, related to spatial coding ('where' pathway), follows a route including the postrhinal cortex (POR) and the medial entorhinal cortex (MEC) to reach the HPC. Even within the HPC, information from these different pathways remains largely separated, projecting to different subparts of CA1.

The spatially extended responses we observed in chapter 4 do not seem to fit the classical functions described to PRH or the 'what' pathway coding for object features and recognition memory. This raises the following questions; What

is represented by these extended activations and deactivations and how 'spatial' are these responses which seem to be locked to spatial segments of the maze, e.g. left or right side arm? Alternatively, one could ask how separated these two pathways really are.

To answer these questions, we should take a closer look at both the anatomy and functions ascribed to the PRH.

Definition of the rodent perirhinal cortex

Borders. The precise borders of the PRH in rodents have long been subject to debate. As a result it not always easy to compare studies regarding the PRH. During the second half of the 90s and early 00s Burwell, Amaral and colleagues published a series of papers in which cytoarchitectonic, histochemical and connectionist criteria were used to define the borders of the perirhinal and postrhinal cortices in rats, see Figure 2A. These definitions have greatly helped to standardize the nomenclature in the current literature enabling better comparisons between papers from different labs. In our research and in the remainder of this work I will stick to these definitions.

In rodents, PRH is comprised of Brodmann areas 35 and 36. Areas 35 and 36 are two strips of cortex situated along the posterior quarter of the rhinal sulcus. Generally, area 35 is situated at the ventral bank while area 36 is positioned at the dorsal bank of the rhinal sulcus. At the posterior end, the PRH curves a bit dorsally, such that at the posterior end area 35 is also positioned dorsal to the rhinal sulcus. Area 35 is agranular, lacking layer IV, has a thick layer I, and large heart-shaped cells in layer V. Area 36 in comparison has a thin layer IV and larger layer II with patches of increased cell density.

The PRH is rostrally bounded by the insular cortex. The posterior end of the claustrum corresponds the most rostral part of the PRH. Posterior, areas 35 and 36 transition into POR. This transition is marked by ectopic cells in layer II, encroaching into layer I. Ventral from area 35 and POR is the entorhinal cortex (EC). The EC can be recognized by the lamina dissecans, a sparsely populated layer VI. Dorsally, both area 36 and POR border with temporal association cortex (TEA). It is not trivial to cytoarchitectionally distinguish TEA from area 36. TEA has more small pyramidal shaped cells in layer II compared with area 36, which has more round shaped somas. In addition, TEA sometimes has a lower cell density around layer V (Burwell et al., 1995; Burwell, 2001; Furtak et al., 2007b).

Immunohistochemically, using staining for heavy metals by using Timm's method or by staining for parvalbumin, the border between area 35 and EC is very clear, by the respective increase (Timm's) or decrease (parvalbumin) of staining in the PRH. Dorsally the transition between area 36 and TEA is more transient, but still clearly marked by a decrease (Timm's) or increase (Parvalbumin) of staining in TEA with respect to PRH (Burwell et al., 1995).

Afferents and efferents of the perirhinal cortex. About half of rodent PRH afferents originate in cortical areas, while the other half carries subcortical inputs.

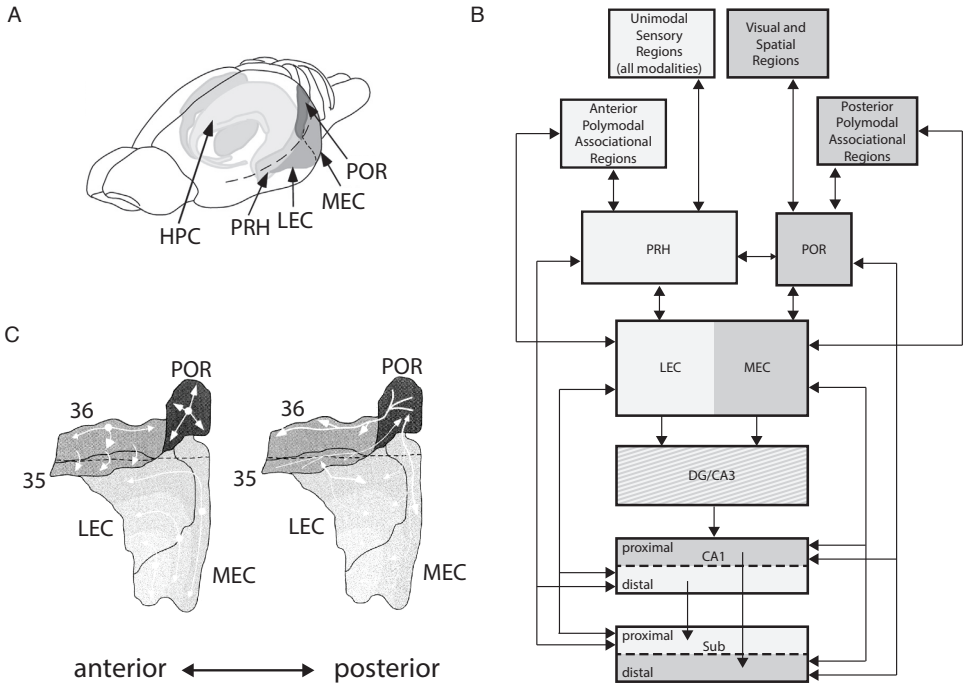


Figure 2 | Perirhinal cortex projections. A) Anatomical overview of medial temporal lobe structures in the rat. The perirhinal cortex (PRH), postrhinal cortex (POR), lateral entorhinal cortex (LEC), medial entorhinal cortex (MEC), and hippocampus (HPC) are shown. The horizontal dashed line indicates the rhinal sulcus. Image was adapted from Agster et al. 2013. B) Schematic overview corticohippocampal connections. Direct and indirect inputs to the CA1 subfield of the hippocampus and subiculum (Sub) are shown for the PRH-LEC (light grey) and POR-MEC (dark grey) pathways. C) Unfolded maps of parahippocampal areas in the rat showing patterns of intrinsic (left) and inter-areal connections (right). The perirhinal cortex is separated into area 35 and area 36. Intrinsic connections within area 36 spread throughout the anterior-posterior extent of the PRH. Projections from area 36 to area 35 are largely restricted to the same anterior-posterior location. A similar pattern is seen in projections from area 35 to the LEC and POR to MEC. Different shadings of the LEC and MEC show regions with different septotemporal hippocampal projections. Light grey indicates projections to the most septal half of the hippocampus. The arrow indicating the HPC in panel (A) points towards the septal pole of the hippocampus. Darkest grey LEC and MEC areas in (C) project to the most temporal parts of the hippocampus (parts of the HPC closest to the PRH). The images in (B) and (C) were adapted from Burwell (2000).

Area 35 receives most projections from the EC, piriform cortex, insular cortex, and the amygdala. Area 36 receives major projections from temporal association areas - subserving all different sensory modalities -, insular cortex, EC, and amygdala (Burwell et al., 1995; Furtak et al., 2007b). The PRH has return projections to all input areas. The ratio between afferents and efferents differs per input area.

Both area 35 and 36 receive inputs from medial frontal areas. These projections follow a rostro-caudal gradient. The infralimbic cortex targets the most frontal areas of area 35 and area 36, the prelimbic targets medial area 35 and the anterior cingulate cortex predominantely targets the more caudal parts of area

35 and 36 (Deacon et al., 1983; Jones and Witter, 2007). Both area 35 and 36 send strong return projections to the medial frontal areas.

The amygdala has dense connections with the PRH. PRH receives strong projections from basal, accessory basal and lateral nuclei. These projections target area 35 more than area 36 according to Pitkänen et al. (2000) and Pikkarainen and Pitkänen (2001) - although Furtak et al. (2007) report more amygdala inputs towards area 36 compared to area 35. Return projections from PRH to the amygdala are equally numerous and target the same areas with the strongest projections going to the lateral nucleus. Area 36 projects more strongly to the amygdala than area 35 does, even though both have substantial efferents to the amygdala.

Somatosensory input from the barrel cortex is projected throughout the whole rostro-caudal axis (Naber et al., 2000) of PRH. In accord with its anatomical position, area 36 receives more input from the temporal association areas than area 35, with the visual association cortex targeting only caudal parts of area 36. Visual association areas predominantely target POR. POR in turn projects to the whole rostro-caudal extent of area 36, but it only shows weak connections to area 35. Olfactory inputs from the piriform and periamygdaloid cortices on the other hand preferentially target area 35 over area 36. This again follows the anatomical proximity of area 35 and area 36, with area 35 positioned ventral from area 36 and the piriform cortex ventral and anterior-ventral from area 35 (Deacon et al., 1983; Burwell and Amaral, 1998; Burwell, 2001).

Superficial neurons in area 35 and area 36 project to the entorhinal cortex, with a large majority of projections terminating in the lateral entorhinal cortex. Area 35 has stronger connections to the EC than area 36. There are also return projections from the EC to PRH, but these connections are much weaker than the forward connections. EC projections originate most strongly in the rostral PRH.

Finally, the PRH also has direct connections to the hippocampus, see Figure 2B. Superficial cells in PRH directly target the distal parts of CA1 and the proximal parts of the adjacent subiculum (Naber et al., 1999; Witter et al., 2000; Witter et al., 2000). These projections likely originate mostly from area 35, which has more hippocampal efferents than area 36 (Furtak et al., 2007b). Return projections from these same areas predominately target deep cells in the PRH (Deacon et al., 1983).

Broadly speaking PRH inputs and outputs follow a cascade from the sensory cortex to the hippocampus. TEA projects laterally to the whole rostro-caudal extent of area 36. Within area 36 there are rostro-caudal projecting cells to other parts of area 36. Projections from area 36 to area 35 and projections from area 35 to the entorhinal cortex again mostly stay within their rostro-caudal bands (see Figure 2C; Burwell, 2000).

Where the PRH predominantly targets the lateral part of the entorhinal cortex, POR projects to the medial part of the entorhinal cortex (see Figure 2B; Naber et al., 1999). Analogous to the PRH, POR also has direct connections with the HPC. In contrast to the PRH, POR efferents project to proximal CA1 and distal subiculum.

These targets mirror the direct inputs from LEC and MEC to CA1 of the hippocampus (Naber et al., 2001). Similar to PRH, LEC projects to distal CA1 and proximal subiculum, while MEC, in concert with POR, targets proximal CA1 and the distal subiculum. Thus, these short cuts to the hippocampus maintain the segregation of pathways.

Given the prevalence of visuospatial inputs to POR (Burwell and Amaral, 1998) and the discovery of spatial responses in the MEC in the form of grid (Fyhn et al., 2004; Hafting et al., 2005), border (Savelli et al., 2008; Solstad et al., 2008), and head direction cells (Taube et al., 1990; Sargolini et al., 2006), the MEC, and the associated pathway are deemed important for spatial processing.

The LEC on the other hand receives inputs from the assumed non-spatial, object oriented PRH. This same distinction is seen in the different target areas in CA1. While the whole dorsal CA1 contains place fields, place fields in proximal CA1, receiving direct inputs from MEC and POR, are more stable and carry more spatial information than place fields in distal CA1 (Henriksen et al., 2010). Combining these observations has led to the hypothesis that there are two physical and functionally distinct pathways.

Functions of the perirhinal cortex - Recognition memory

Being part of the MTL, PRH has traditionally been associated with recognition memory (see introduction; Buckley and Gaffan, 1998a, 1998b, 2006; Mumby et al., 2002; Bowles et al., 2016; Duke et al., 2017). Lesions to the PRH impair novelty judgements. The most commonly used object recognition task, the delayed non-match to sample task (DNMTS, see Figure 3), is comprised of two phases (Ennaceur and Delacour, 1988). During the initial sample phase, the animal sees (in monkeys) or is allowed to explore (in rodents) two objects. These objects can either be the same or different. In a subsequent recognition phase one of the two objects is changed. Monkeys are asked to select the new objects, while rats are set to explore again. This task makes use of the innate preference rodents have to explore new objects. A reduction in absolute or relative time spent exploring the previously encountered object indicates familiarity. Continuous versions of this task also exist, see Figure 3E-F. In these tasks, what was the old object in trial 1 will get replaced, such that what was the new object in trial 1 is now the old object in trial 2. This provides a internal control since each object is presented twice (once as the novel object and once as the familiar one; Albasser et al., 2010). A major advantage of this type of task is that analogue versions of this task can be used in rodent, monkey and human studies. In rodents, impairments are shown by a failure to preferentially explore the new object over the old one. Humans and monkeys can be trained to manually select the novel object.

Rats with PRH lesions are impaired in delayed object recognition tasks. Different versions of the DNMTS task can be used to explore different features of recognition. For instance, one can make this task spatial, by changing the location of the objects instead of changing their identity, see Figure 3B. PRH has been shown to

be important in the object recognition version of this task, but not in the spatial version or different spatial control tasks, like delayed alternation tasks on a T-maze or tests in a Morris water maze. Opposite effects have been observed with HPC lesions showing no impairment in object recognition tasks and severe impairments in spatial versions of the object recognition tasks. Double dissociations between the PRH and HPC and their respective functions in object or spatial coding are numerous throughout the literature (Brown and Aggleton, 2001; Burwell et al., 2004; Winters et al., 2004; Winters and Bussey, 2005; Aggleton and Brown, 2006; Saksida et al., 2006; Abe et al., 2009; Barker and Warburton, 2015; Hernandez et al., 2015; Nelson et al., 2016). Again, this supports the dual pathway hypothesis.

Single unit recordings in the PRH have shown that neurons are sensitive to the prior presentation of objects. Neurons in the PRH decreased their firing rate for familiar objects with respect to new objects (Zhu and Brown, 1995; Young et al., 1997; Brown and Banks, 2015; von Linstow Roloff et al., 2016). These findings are supported by immediate early gene studies in which exposure to new objects led to increased c-fos expression (Zhu et al., 1995). Also here, PRH seems to be object-oriented since placing the rats in a new environment did not increase immediate early gene expression in PRH, but it did in the HPC. Interestingly, when scenes of familiar objects were rearranged, PRH did show activations, but HPC did not (Zhu et al., 1995, 1997; Aggleton and Brown, 2006).

Novelty signal. Despite the well-researched role of the PRH in recognition memory it remains up for debate where, in the brain, the novelty signal comes from. Is the novelty signal a product of the PRH or can novelty signals also be provided by different areas? PRH lesions consistently result in deficits found during the recognition phase. Initial exploration during the sample phase is conducted as normal. During the recognition phase, however, PRH lesioned rodents fail to preferentially explore the novel object over the familiar one. Both the new and familiar object are explored equally. This lack of a difference can be interpreted in two ways: 1) the novel item is erroneously perceived as familiar or 2) the familiar item is not recognized and is therefore treated as novel. To investigate these two possibilities McTighe et al. (2010) used a simplified version of the spontaneous recognition task. Instead of presenting the novel and familiar object simultaneously during the recognition phase, pairs of either novel or familiar objects were shown. PRH lesioned animals are equally impaired in this version of the task, showing reduced exploration of novel objects. This reduced exploration could indicate that the animal incorrectly recognizes the new objects as familiar; false memory. McTighe et al. (2010) showed that by placing rats in a dark environment, instead of a holding cage, they could rescue performance in the PRH lesioned animals. They hypothesise that PRH lesions induce an increased susceptibility to outside stimuli, causing interference during the delay. Without the PRH's ability to maintain integrated complex representation of stimuli, animals have to make use of simplified feature-based representation. Exposure to a general environment containing simple

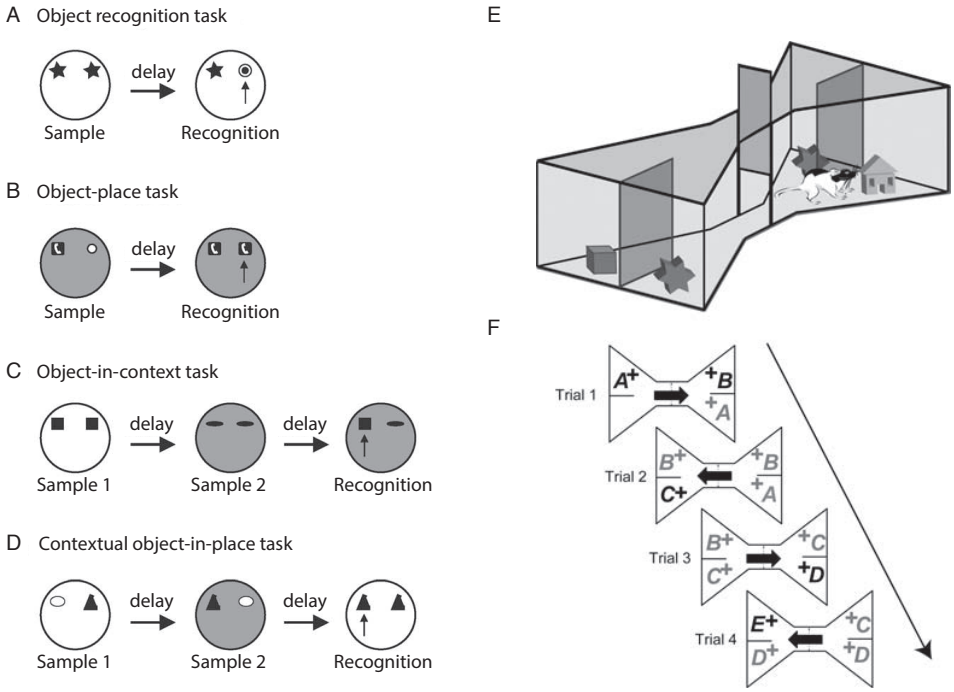


Figure 3 | Different versions of the delayed non-matching to sample task. A-D) Different versions of the delayed non-matching to sample task (DNMTS). During one or two sample phases the animals explore different object and context combinations. Objects are encoded by shapes and context is represented by different shadings. After a variable delay the animal is returned for the recognition phase. Here the animal has to discriminate A) the unfamiliar object, B) the new object-place pairing, C) the new object-context pair, or D) the new object-location-context pairing, indicated by the arrow. Image was adapted from Langston and Wood (2010). E-F) Continuous version of the object recognition task. In these bow-tie shaped mazes the animal explores two objects on one side of the bow-tie (or one in the first trial A+). During this exploration the door to the other side of the maze is closed. After a variable delay the animal is allowed to move to the other side to explore the two objects there (A+ and B+). In consecutive trials the new object is repeated while the previously seen object is replaced by a new object. This way every object is the target (novel, bold letters) and the distractor (familiar) object once. Image was adapted from Albasser et al. (2010).

features, lines and corners, could interfere with the simple object representations.

Albasser et al. (2015) tested McTighe's findings using a continuous delayed non-matching to sample task. Similar to the findings by McTighe et al. (2015) they found that PRH lesioned rats showed reduced exploration for novel objects. Contrary to McTighe's predictions they only found a marginal effect of proactive interference caused by the presentation of an extra set of two objects before the recognition phase. This effect was not as strong as would be predicted by McTighe's results and there was no indication that interference increased over time. In the continuous version of the delayed non-matching to sample task the animal encounters many stimuli in the course of a session. Lesioned animals were impaired in performance when compared to controls, but they still performed above

chance. If substantial proactive interference would lead all novel stimuli to appear familiar, performance should have plummeted.

In a follow-up on Albasser et al. (2015), Olarte-Sánchez et al. (2015) used a variation on the simple task designed by McTighe et al. (2010). Instead of showing only two novel or two familiar objects during the recognition phase, they showed both the pairs of novel and familiar objects sequentially. PRH lesioned animals could perform this task normally. By showing that PRH lesioned animals could still perform the simplified version of the novelty detection task, they showed that PRH is not required to create novelty signals. As such Olarte-Sanches et al. (2015) propose a role for the PRH in both unifying features into objects and attaching a novelty signal to these percepts. Lesioning PRH weakens the coherence of object features and the associated novelty/familiarity signals, resulting in unstable percepts which are vulnerable to task complexity.

Functions of the perirhinal cortex - Perception

Apart from its classical role in recognition memory, PRH has in more recent years been shown to be involved in perception. In PRH lesioned rats, object recognition is often shown to be spared when the delays are short (< 10-40 min), however when the delays are increased these animals display impaired performance (Otto and Eichenbaum, 1992; Ennaceur et al., 1996; Ennaceur and Aggleton, 1997; Norman and Eacott, 2005). Other studies have shown that impairments can also be present at zero or at very short delays (Bartko et al., 2007; Albasser et al., 2015). Norman and Eacott (2004) report that the duration of delay which can be bridged without a PRH is dependent on the complexity of the stimuli. Rats could bridge very long delays when presented with distinct objects, but if the objects were manipulated to be very similar, the duration decreased to less than 5 minutes. This fits with results from Bartko et al. (2007), who report zero delay deficits for PRH lesioned rats in an oddity discrimination task, where the stimuli were explicitly manipulated to be perceptually similar.

These findings are corroborated by findings from the monkey literature which show that the perirhinal cortex is important both for recognition memory and for resolving feature ambiguity (Meunier et al., 1993; Buckley and Gaffan, 1998b; Buffalo et al., 1999; Bussey et al., 2002; Bussey and Saksida, 2005; Saksida et al., 2006, 2007; Bussey and Saksida, 2007; Ahn and Lee, 2017). Bussey et al. (2002), tested control and PRH lesioned monkeys in a visual paired associate task. They used pairs of pictures as single stimuli. In a low feature ambiguity trial, they were trained that pictures A and B together and C and D together were the rewarded, positive conditioned stimulus (CS+). Pictures EF and GH corresponded to the non-rewarded, negative conditioned stimulus (CS-). During testing the animals were presented with a combination of CS+ and CS- (e.g. AB and EF or AB and GH). The monkeys had to select the CS+ to receive a reward, which was AB in our two examples. In this low ambiguity version of the task all pictures constituting the conditioned stimuli were different between CS+ and CS-. In high ambiguity trials,

the monkeys were trained with AB and CD as CS+ and BC and AD as CS-. Here, all individual pictures are both part of the CS+ and the CS-. In the hard, high ambiguity, version, information from both images needed to be combined in order to make the correct choice. Lesions to the perirhinal cortex severely impaired monkeys in this task.

Single unit recordings in monkey TEA and PRH showed a similar role for the PRH in creating item or feature associations (Suzuki and Naya, 2014; Eradath et al., 2015; Naya, 2016). A series of studies of the Miyashita lab has shown that there is a progression in complexity of coding item-item associations in a delayed paired associates task from TEA to area 36 and area 35. In this task animals initially learned to pair sets of pictures. In subsequent association trials, they were shown one picture of a learned pair. After a delay two pictures were presented: the paired associate of the initial stimulus and a distractor image belonging to a different pair (Sakai and Miyashita, 1991).

Naya et al. (2003a) recorded in TEA and area 36. They reporteded that neurons in both areas display stimulus selective responses. Area 36 showed more neurons which code for both stimuli in a pair than TEA (33% and 5%, respectively; Naya et al., 2003a). This coding for pairs arose simultaneously with their stimulus selectivity. During the delay, neurons in TEA preferentially coded for the paired associate of the stimulus they had just observed, while area 36 neurons maintained representations of both the cue and the target stimulus (Naya et al., 2003b). In a later study by Fujimichi et al. (2010), responses in area 35 were also measured. In this study, they showed that area 35 also codes for stimulus pairs. In area 36 neurons which are active during the delay coded for both objects in a pair, but kept a distinction between the two objects. Delay neurons in area 35, however, did not distinguish between the two stimuli anymore. This is suggestive of increased association and unitization of different concepts into a single whole in a pathway leading from TEA via area 36 to area 35.

Cross modal object recognition. Animals can also learn a cross-modal version of the DNMTS task, see Figure 4A. Here rats either sample in the dark (using their whiskers and presumably using odour as well) and have to do recall in the light with a translucent plate before the objects (preventing the use of whiskers) or vice versa. Lesions to the PRH resulted in a deficit in cross-modal object recognition, while lesions of the fornix or HPC had no effect (Albasser et al., 2010; Reid et al., 2012). Rats with PRH lesions were not only impaired in the cross-modal version, but also showed a deficit in the visual-only version. However, they did not show an impairment in olfactory- or tactile-only versions of the same task (see Figure 4A; Winters and Reid, 2010). Lesions to the posterior parietal cortex (PPCx) showed an inverse pattern of impairments. These animals were similarly impaired on the cross-modal object recognition task, but showed normal performance in the visual version, while being impaired in the olfactory and tactile versions of the DNMTS task.

In 2011, Albasser et al. reported a similar pattern of impairments in a delayed cross-modal object recognition task. In contrast to Winters and Reid (2010), they did not block the objects in the visual-only condition. Instead cross-modality was achieved by turning the light on and off (blocking visual inputs), while not manipulating tactile inputs. Animals would either sample in the light and recognize in the light, sample in the light and recognize in the dark, sample in the dark and recognize in the light, or sample in the dark and recognize in the dark. Control animals displayed no impairments in this task, showing a natural ability to integrate information from different senses. PRH lesioned animals showed deficits in all conditions, except when both sampling and recognition occurred in the dark. The dark-dark condition is the only condition without a visual element. Here the animals presumably solve the discrimination using the available tactile or olfactory input. These same cues are also present in the other versions of the task, however in any condition involving light the rats were impaired. The visual inputs seem to interfere with other modalities.

Albasser et al. (2011) hypothesised that PRH lesioned animals show a bias toward using visual information, which is only lifted when visual information is absent, allowing the use of olfactory and tactile cues. However, the authors do not explain why PRH lesioned rats are also very impaired in the light-light condition. A bias towards visual information alone cannot explain these results. In addition to a bias towards visual information these results also point towards deficiencies in processing of visual information. This is a peculiar pattern of defects. If PRH lesions result in selective deficits in the visual processing, why does it also lead to prioritizing vision over other tactile and olfactory domains, which are still functional, as demonstrated by the dark-dark condition? This could be an overly anthropomorphised question. There is likely no choice for the rat. Instead, lesioning the PRH could remove an inhibitory pressure on visual inputs. Lesioning the PRH could result in an excess of non-integrated visual information. Alternatively, PRH may be important when there is competition between multiple sensory inputs. PRH could be important for inducing a bias towards non-visual information.

Additionally, the PRH/PPCx inactivation results seem to be at odds with previous findings indicating a role for the PRH in integration of sensory stimuli and showing relatively minor visual inputs to the PRH (Burwell and Amaral, 1998). The lack of PRH involvement could be due to the unimodal nature of the task used in Winters and Reid 2010. To test this Jacklin et al. (2016) tested the effect of multimodal pre-exposure to visual, tactile, and cross-modal object recognition. Previously Reid et al. (2012, 2014) have shown that multimodal, but not unimodal pre-exposure facilitates performance on the cross-modal task by increasing the retention time in control animals. The pre-exposure was performed prior to inactivation of PPCx or PRH. Pre-exposure abolished the effects of PPCx inactivation shown by Winters and Reid (2010). Animals which were pre-exposed to the objects before receiving PPCx lesions now performed similarly to controls in all conditions. PRH inactivation on the other hand now produced impairments across all tasks; visual only, tactile only, and cross-modal. Even a single short pre-exposure to the

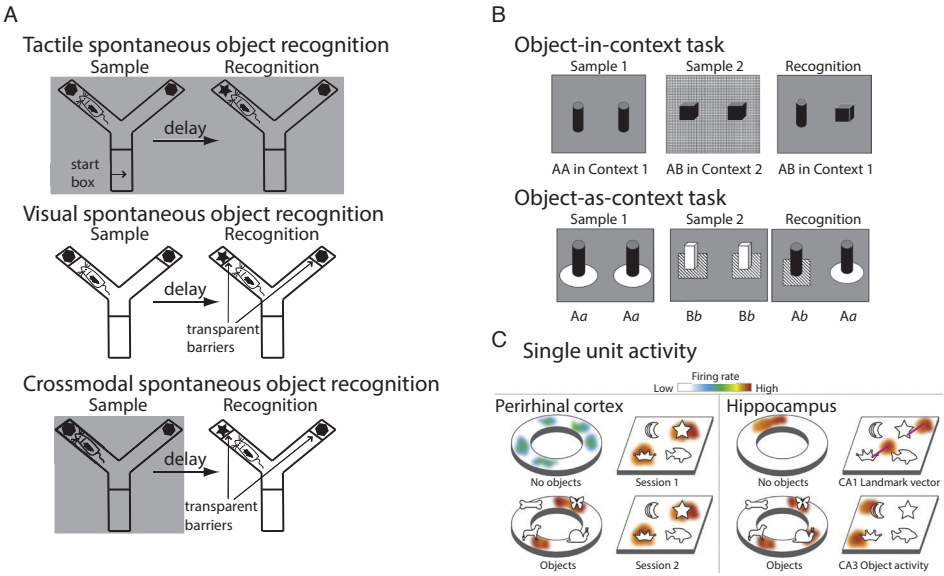


Figure 4 | Testing perirhinal cortex activity using different tasks. A) Tactile, visual and cross-modal versions of the spontaneous object recognition task. In these tasks exploration of novel and familiar objects is measured. Healthy animals preferentially explored novel objects over familiar objects. Animals can integrate information from different senses to perform these tasks. In the dark condition (dark grey) the lights were turned off to prevent visual inputs. During the light condition the objects were blocked by transparent barriers to avoid tactile and reduce olfactory input. Image was adapted from Winters and Reid (2010). B) Object-in-context recognition. The top row shows the classic object-in-context test. In the bottom row a second object a or b was used as a context. Test objects A and B were stacked on top of the context objects. PRH lesioned animals showed increased impairments in this object-as-context task. Image was adapted from Norman and Eacott (2005). C) Examples of single neuron responses to space and objects in the perirhinal cortex and CA1 of the hippocampus. Perirhinal cortex neurons showed diffuse spatial responses on the circle. When objects were introduced to the track neuronal responses in the perirhinal cortex locked to the objects. Similarly, perirhinal responses were also locked to objects in open fields. These representations were stable across sessions. Hippocampal neurons showed spatially selective responses on empty tracks. When objects were added, CA1 neurons showed activity at or near the objects. In open fields CA1 firing can also be locked a fixed distance away from objects, indicated by the red lines. CA3 activity is often found closer to the objects. CA3 neurons do not show activations at fixed distances away from the objects. Image was adapted from Burke and Barnes (2015).

multimodal stimulus seemed to allow the formation of a multimodal abstract representation in the PRH which is independent of the PPCx. Interestingly, where in the non-pre-exposed PRH inactivated animals presumably the PPCx could take over to allow tactile object discrimination, this is no longer the case after pre-exposure. Pre-exposure may have resulted in the formation of a representation of the objects, which in a subsequently inactivated PRH prevents recruitment of the PPCx or causes interference, resulting in impaired tactile discrimination. These results seem to confirm the importance of the PRH in binding cross-modal object information in addition to its role in memory. These findings also point to the importance of timing of PRH lesions or inactivations in multimodal processing.

Functions of the perirhinal cortex - Spatial processing

Despite the previously described large body of evidence suggesting double dissociations between the PRH and HPC in object and spatial coding, respectively, there are studies which indicate a role for the PRH in spatial processing as well. A first example of this is found using a variation of the spontaneous object recognition task and the object-place task. In this task animals are often presented with four different objects, placed throughout an environment. After a delay the animals would be shown the same objects in the same environment, but two of the objects have swapped position. Even though all objects are familiar rodents would preferentially explore the two objects which changed location. This task has been shown to depend on interactions between the medial prefrontal cortex, PRH and HPC. Lesions or disruption of any one of these three areas causes severe impairments in this task (Aggleton and Brown, 2006; Barker et al., 2007; Barker and Warburton, 2011, 2015). It is hypothesised though that in this type of task the PRH is mostly involved in coding for object information, while the HPC is important for the spatial component.

Fear conditioning. Despite PRH being classically associated with object-related processing rather than space-related processing, PRH has been shown to have a role in contextual fear conditioning. Large complete lesions to either PRH or POR have been shown to impair freezing in the learned context (Bucci et al., 2000, 2002). Lesioning PRH up to 100 days after conditioning resulted in attenuated fear responses, implying a long-term role for the PRH in representing fearful memories (Burwell et al., 2004). In contrast, HPC lesions have short (1-28 days), but no long-term (28, 100 days) effects on contextual fear conditioning. Fear conditioning to continuous tones was unaffected by HPC lesions (Kim and Fanselow, 1992; Maren et al., 1997). PRH is not involved in fear conditioning to simple continuous tones, but it is required in fear conditioning to more complex discontinuous tones or vocalizations (Furtak et al., 2007a; Kholodar-Smith et al., 2008; Bang and Brown, 2009). This is in line with the perceptual role of the PRH. PRH lesions selectively affect perception of complicated, but not simple stimuli (Eacott et al., 2001).

Context. In yet another version of the spontaneous object recognition task, the effect of context is measured; the object-in-context task, see Figures 3C and 4B. In this task, a trial is composed of three phases instead of the familiar two. During the first sample phase two of the same objects (AA) are shown in context 1. In the second sample phase two different objects (BB) are shown in context 2. Context 1 and 2 differ in both colour and texture on the walls and floors. The location of the objects in space is held constant. During the recognition phase, one of each object pair (AB) is placed in one of the contexts, e.g. context 1. During recognition both objects are equally familiar, but the object-in-context pairing is new for one of the objects. Healthy control rats will explore the novel pairing over the familiar object-context pair. Norman and Eacott (2005) showed that rats with lesions to either PRH, POR or fornix show impairments on this task when delays of 5 min.

are used. However, when the delay is reduced to 2 min. the POR lesioned animals are selectively impaired over PRH and fornix lesioned animals. When Norman and Eacott (2005) changed the task to use background objects to indicate context instead of wall cues, PRH lesions produced a severe and immediate deficit even at the short (2 min.) delays, while POR and fornix lesions did not. In this version of the DNMTS task, object-as-context, objects A and A were stacked on top of context objects a and a, see Figure 4B. During the second exploration phase objects B and B were stacked on context objects b and b. During recollection objects A and B were both presented on top of one of the context objects (e.g. context object a). Similar to the context version, this creates a familiar and a novel pairing, which should be preferentially explored over the familiar pair. Contrary to the context version the object-as-context version is more reliant on PRH functioning.

Lesions to the HPC did not affect the object-in-context task (Langston and Wood, 2010). They do affect performance in an allocentric object-in-place task and a contextual version of the object-in-place task (see Figure 3D).

Disconnecting PRH from POR by crossed (contralateral) lesions impaired performance on the object-context task but had no effect on contextual fear conditioning (Heimer-McGinn et al., 2017). This could suggest that there are several cortical/subcortical pathways which assist in associating context with stimuli: one which requires both PRH and POR and one in which the interaction between PRH and POR is not necessary.

In contrast to the contextual fear studies by Bucci et al. (2000) and Burwell et al. (2004), Heimer-McGinn et al. (2017) lesioned rats before acquisition. This could explain the lack of effect on contextual fear conditioning in a way similar to the above-mentioned results, showing that pre-exposure to multisensory objects makes the memory trace more PRH dependent. Second, Heimer-McGinn et al. (2017) made crossed lesions leaving PRH in one hemisphere and POR in the other available. The remaining PRH and POR cortices could facilitate other areas in learning context in the highly salient fear conditioning tasks.

Another observation concerns parsing of the environment. In contextual fear conditioning tasks the closest (most proximal) cues are the contextual wall cues. The animals are situated in an otherwise empty chamber. In the object-in-context task, there is a proximal cue (the object) and a more distal cue (the context), which need to be parsed. In the previously described object-as-context task, used by Norman and Eacott (2005), this boundary is not as clear, see Figure 4B. The animals could either integrate the two stacked objects into a single compound object, or the rat could keep the cues separate and assign different values. If the objects are maintained separately (one as test object and one as contextual cue) the contextual object could be a discrete mini context or it could be integrated with the larger testing surroundings, i.e. the neutral testing box. The additional involvement of the PRH in the object-as-context task could be due to increased complexity due to the addition of a 3rd item to integrate (context object, on top of the test object and the general context). Alternatively, addition of a more distinct

local cue can more actively recruit PRH compared to a global background cue.

This raises the question how integrating features or objects works. When is something part of an object or a compound object and when is it just part of the surroundings? This question is akin to the perceptual figure ground segregation, however here I would like to focus on object segregation, not the perceptual segregation problem.

Without raising a philosophical debate about the definition of context, an intuitive argument could be made that stacked objects are more easily unitized than an object and the floor, especially given that floors and walls are possibly already integrated into a separate room object in the relatively small operant chambers which are commonly used.

Allocentric spatial memory. The effects of PRH lesions on spatial memory have also been tested in tasks outside operant chambers. Ramos and Vaquero (2005) trained rats with PRH lesions, on a plus maze, to always go to a designated goal arm (e.g. the west arm). Animals started each trial randomly in one of the other three arms and needed to use allocentric spatial information (room reference frame) to orient themselves and find the target arm. In this experiment, Ramos and Vaquero (2005) showed that PRH lesions did not affect acquisition and short-term retention (24 hours) of the task. Interestingly the PRH lesioned animals started showing impairments in retention after very long delays (74 days) and showed very poor relearning of the task, indicating a role for PRH in long term spatial memory.

Apart from these long-term effects, most studies with pre-training lesions report only mild short term or no effects of PRH lesions in allocentric tasks (Wiig and Bilkey, 1994; Liu and Bilkey, 2001; Ramos, 2013a). A few experiments have been conducted where the rats were lesioned after the initial acquisition of an allocentric task. Abe et al. (2009) showed that while PRH lesions led to larger impairments in object recognition tasks, PRH lesions also impaired previously learned place discriminations, but not similar newly learned place discriminations. Congruent with these results, Ramos (2013b) also showed a timing dependent deficit of PRH lesions in the previously described allocentric task. Rats were trained to use allocentric cues to find the rewarded arm in the plus maze. After training, the animals received PRH lesions. Similar to the results found by Abe et al. (2009), Ramos et al. (2013) found that animals were impaired in the previously learned task compared to sham operated controls. However, they were able to learn the task in a new allocentric context and retain this information across 15 days.

In a recent follow up study, Ramos (2017) tested navigation strategies used by PRH lesioned animals. He tested animals on two versions of the plus maze task. In the first version, the animals always started in the same start arm. Thus, the goal arm could be found by using either an allocentric strategy, using distal room cues, or an egocentric motor strategy, using body turns. During testing, the animal started each trial in one of the other two start arms. In the second experiment animals could find the goal arm either by using a large constellation of distal

landmarks (allocentric) or an intra-maze stimulus (sandpaper covered floor; stimulus-response). In this task, the animals started each trial out of one of the three start arms. During testing the intra-maze cue was shifted around with respect to the baited goal arm. In these two experiments Ramos found that PRH lesioned animals predominantly used non-allocentric strategies. In contrast, in both tasks, healthy controls mostly used allocentric strategies. This could hint at a role for PRH in allocentric spatial strategies. Even though PRH may facilitate allocentric strategies, it is not required for allocentric spatial memory. PRH lesioned animals preferred non-allocentric strategies, but they did also use them (Ramos, 2017). Alternative neuronal circuits can fill in functions performed by PRH cortex in healthy animals when the PRH is damaged.

Single unit responses in the perirhinal cortex

Single unit responses in the PRH have been shown to code for objects and their familiarity in awake monkeys (Fahy et al., 1993; Xiang and Brown, 1998) or anaesthetized rats (Zhu and Brown, 1995) by decreasing the firing rates during repeated exposures as objects become more familiar. There is, however, also a study by Hölscher et al. (2003) which shows increases in firing rates in PRH of macaques after extensive exposure to objects (>400x).

These studies were performed on restrained or anaesthetized animals. Single unit recordings from rats exploring a plus maze (Burwell et al., 1998) or circular arena (Burke et al., 2012) show fairly consistent, but diffuse spatial firing fields. Rotating a plus maze with different floor patterns in each arm showed that these firing fields did not rotate with the environment, whereas place fields do (O'Keefe and Conway, 1978; Muller and Kubie, 1987). Instead, they remapped in an unpredictable way. When objects were placed in the circular arena (Burke et al., 2012), PRH firing locked to the objects. Most units displayed elevated firing around multiple objects, see Figure 4C. These firing fields ('object fields') were highly consistent within a session and fairly stable across sessions. About 40% of the units showed stable firing fields across sessions when the location and identity of objects were held constant. When the objects were changed (identity, not location), roughly 30% of PRH neurons still maintained their object fields. In a study where rats foraged in an open field with multiple objects, similar patterns were observed. PRH firing was related to objects. When an object was added, or moved to another location, firing patterns of PRH units changed to incorporate the changed object and previous firing fields associated with the old location were lost (Deshmukh et al., 2012). Burke et al. (2012) quantified firing rates for initial and subsequent encounters of the objects, but they did not find novelty-related changes in pyramidal cell firing, despite increased object exploration during the first two laps. Firing rates of pyramidal cells were similar for the object and no-object conditions. In a follow-up study using the same task Maurer et al. (2017) again showed no difference in firing rates for the object versus no-object condition in pyramidal cells. Looking at interneurons, however, they did find an increase in average firing rate when objects were present.

In these previous studies the objects were not associated with reward. They were part of the environment or formed obstacles the animals needed to walk around, while the animal foraged or walked back and forth on a track to obtain rewards at each end. Von Linstow Roloff et al. (2016) argue that spontaneous object recognition may not be the best task to find neuronal novelty responses. They tested the same rats in both a paired viewing task with objects being displayed on computer screens and in a spontaneous recognition task. They found novelty related changes in firing rates (73% showing a decrease in firing rate over repetition) in the paired viewing task, but not in the spontaneous object recognition task. Von Linstow Roloff et al. (2016) argue that the novelty signals could be fleeting and novelty signals could average out during the relatively long bouts of exploration seen in the object recognition task, compared to the short presentations on the computer screens.

Another important factor for engaging the PRH could be the presence of reward contingencies. PRH neurons have been found to change firing patterns in response to reward schedules and reward delivery (Liu and Richmond, 2000; von Linstow Roloff et al., 2016). In the paired viewing task rewards were delivered at the end of the stimulus presentation. In contrast, during the spontaneous object recognition task reward pellets were randomly dropped 1-4 s after picture offset.

When parahippocampal region (PHR, which includes PRH, POR and EC) activity was investigated in stimulus-reward tasks, like an odour driven non-matching to sample task, and PRH activity was recorded during an object cued spatial choice task, these areas were shown to activate to all different task components. To cite Young et al. (1997) on the general behaviour of parahippocampal neurons: 'Nearly every neuron fired in association with some trial event, and every identifiable trial event or behavior was encoded by neuronal activity in the PHR'. Ahn and Lee (2015) mention this regarding PRH activity: 'The firing rates of perirhinal cortex neurons were significantly modulated by critical events in the task, such as object sampling and choice response'. The latter study shows that PRH did not only respond to the objects, but also to the combination of objects and the subsequent spatial response, touching a left or right patch on a centrally positioned touch screen. This is in line with the previously described function of PRH in binding features of objects. In this case, however, it is not a physical feature, but a task rule which is combined with a stimulus or object representation (Suzuki and Naya, 2014; Naya, 2016).

Similar to the studies mentioned above we observed PRH firing correlates for all different events during a trial on the figure-8 maze (sound cue, image, sandpaper, reward), see chapter 4. However, on top of these responses we found sustained activations spanning different components of the maze (one side arm, both side arms, middle arm). An important difference between our study and the studies described above is that we used both an active task with clearly defined reward conditions and a setup which consisted of multiple walkways, instead of a single path or an open field. The figure-8 maze can be divided into different spatial

segments. The middle arm is delineated by doors on either side. These doors are closed throughout the relatively long inter-trial intervals (15-25 seconds). When released from the middle arm the rats are required to make a choice between the left and right side-arms. Once the rats progressed through roughly 1/3th of the side arm they were blocked if they attempted to walk back into the opposite arm. Finally, after the reward the animals were required to walk back into the middle arm. Here again the exit of the opposite side arm was blocked, such that the rat could only move into the middle. Due to this procedural blocking off of different paths the setup was naturally divided into three segments. A similar natural segmentation did not apply in the tasks described by Burke et al. (2012), Deshmukh et al. (2012) and Ahn and Lee, (2015).

Keene et al. (2016) published a study in 2016 which included single unit recordings from the PRH during a context guided olfactory association task. In this study rats were trained to dig for reward in one of two cups with scented sand. The cups of sand were positioned in one of two square arena's (contexts) which were linked by an alleyway. The context determined which of the two cups was baited. In context A, the cup (object) with scent 1 contained a reward, while in context B reward could only be found in the cup with scent 2. The position of the cup within the context did not matter, e.g. whether the cup with scent 1 was to the left or right of the other cup. Consistent with previous reports Keene et al. (2016) showed PRH responses to both object (16.5% of recorded PRH cells) and object x location (28%). Interestingly, in addition to these object responses, 29.9% of PRH cells differentiated between the contexts. Inversely they also reported object coding in the MEC. In fact, Keene et al. (2016) found that in contrast to the what-where distinction, the PRH, LEC, and MEC all coded for objects, locations and contexts. PRH and LEC differed from MEC in the strength of object versus location coding, with the PRH and LEC preferentially coding for objects, while the MEC favoured location.

Even though the experimental designs in chapter 4 and Keene et al. (2016) were quite different from each other, the results are complementary. Unfortunately, the single unit PRH responses in Keene et al. (2016) are only plotted in peri-stimulus time histogram (PSTH) fashion, i.e. in the temporal domain. If they would have plotted responses from PRH in the spatial domain as well, they may have shown similar responses to the ones we found.

This is one of the problems of adding a sensory or non-spatial label to an area. Displaying data in multiple domains will help to elucidate the different functions of brain areas. Displaying PRH responses in the spatial domain has possibly revealed a new function for PRH. It is currently not clear how purely spatial our responses are, but they are manifested in the spatial domain.

Deactivations in the perirhinal cortex

Except sustained responses, which seem spatially bounded, another interesting finding in chapter 4 is the prevalence of deactivations in PRH coding (see Figure 5 and Figure 3 of chapter 4). In the place field literature, it is standard that events

are coded by increases in activity. This is because the baseline firing rate of place cells is nearly zero. Thus, any change is by definition an increase. In PRH and many other cortical cells this is not the case. Nevertheless, a stereotyped view of cells changing between an active or silent state is still widely assumed and seen in many examples in figures of neuronal responses in literature. This assumption simplifies interpretations, by binarizing response properties, but also induces an investigator bias. Part of the problem is defining a baseline. A baseline of zero feels 'objective' to the observer and is computationally easy, but many of the neurons we have recorded in the PRH and other cortical areas are rarely silent under baseline conditions, see Figure 5B. Instead, in chapter 4 we have defined the firing rates during the inter-trial intervals, while the rat is kept in the middle arm of the figure-8 maze, as the baseline. When taking firing rate in the middle arm as baseline, it can be readily observed that the PRH uses graded firing, see Figure 5A. Where one unit increases its firing rate for both side arms, another shows a small increase for one side arm and a larger for the other, yet another shows an increased firing rate for one arm, but a decrease for the other and finally firing rate can be decreased in one or both side arms with respect to the middle arm. Firing rates can decrease all the way to zero, but most units do not shut down completely. In short, we have observed different patterns in coding for the middle, left, and right arms.

One interesting observation which we did not show in the paper is that there is a tendency for deactivations to occur during left sided trials (Figure 5B). In all animals, recordings were made from the right hemisphere, presumably favouring processing of information from the left side of the environment, i.e. from the left visual field and left whiskers. Incidentally, during left sided trials the screens were encountered in the right visual field, processed predominately by the left hemisphere, contralateral to the recorded hemisphere. Unfortunately, we do not have recordings from the left hemisphere to investigate if this is a task-related lateralization effect.

As previously mentioned, the PRH is a transition or gateway area between the neocortex and the hippocampal system. However, PRH is not a passive gateway. Instead, PRH is often portrayed as an "inhibitory wall" (Biella et al., 2001, 2002, 2003, 2010; Martina et al., 2001; de Curtis and Paré, 2004; Pelletier et al., 2004, 2005; Unal et al., 2012; Willems et al., 2016). In slice recordings of the guinea pig, inputs from adjacent neocortex are processed by the PRH under a strong local inhibitory control impinging on both excitatory and inhibitory neurons. Long-range connections from more distant neocortical areas or longitudinal inputs from other parts along the rostral-caudal axis of the PRH itself, on the other hand, primarily target excitatory neurons (Martina et al., 2001).

Stimulating the PRH ex vivo in whole brains of guinea pigs by repeatedly electrically stimulating one section of the ventral temporal association cortex resulted in strong response depression in the PRH. When instead two different sections of visual temporal association cortex distributed along the longitudinal axis (ros-

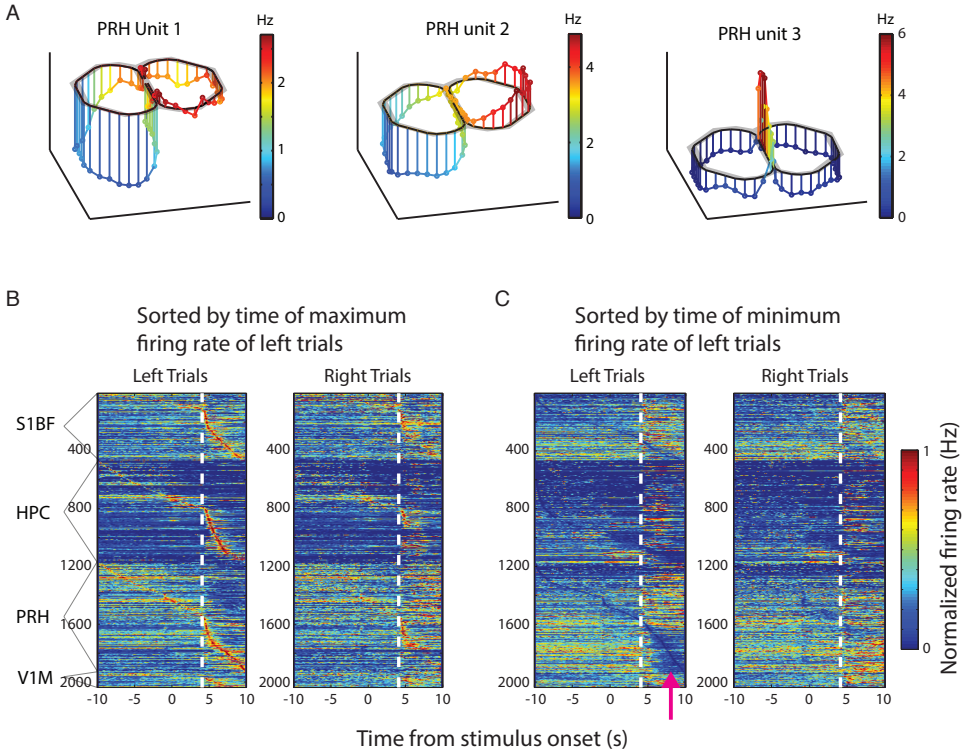


Figure 5 | Deactivations in perirhinal responses. A) Three examples of PRH neurons from the Touch and See dataset (chapter 4), which show decreases in firing rates to one or both of the side arms. Unit 1 shows a decrease in firing rate during left trials with respect to the middle arm and right sided trials. Unit 2 shows both a deactivation for left sided trials and an activation for right sided trials. Unit 3 shows deactivations for both side arms. Image was adapted from Bos et al. (2017). B) Sorted normalized firing rates for all neurons. Firing rates of neurons were normalized by their maximum firing rate and sorted per area based on the time of peak activity for the left trials b) or minimum firing rate. C). Sorting of units was done based on left sided trials and maintained for right sided trials. Time = 0 denotes the onset of the visual stimulus. The white dotted line indicates movement onset. The magenta arrow in (c) indicates a group of perirhinal cortex neurons which all deactivate following movement onset. Timing of the deactivations corresponds to movement through the side arms of the figure-8 maze. The deactivations are specific for left sided trials. Sorting the data based the timing of peak firing on right sided trials does not result in a similar group of neurons upon right trials, data not shown. These results indicate that decreases relative to baseline firing (defined by firing rates in the middle arm) can also be used to code for the different segments of the maze.

tro-caudal) were stimulated simultaneously, responses in PRH were potentiated (Unal et al., 2012). Information from different areas or different longitudinal locations in the same area seems to be required to reduce local inhibition in the PRH to allow response transmission. This response pattern could be especially suited to facilitate integrative functions required in object recognition associated with the PRH.

Even though there is a general consensus that the PRH is controlled by a tight inhibitory drive, this gate has not been widely investigated in relation with its oth-

er functions like object recognition. Therefore, it remains unclear whether the deactivations we have observed could be an expression of this "inhibitory wall" or if another modulatory system is at play.

Irrespective of the mechanism, the observed combination of activations and deactivations served to increase the observed differences between the different segments of the maze, resulting in an improved signal to noise ratio when differentiating between these different segments.

The question remains why there should be increased inhibition preferentially during left sided trials. As mentioned above a possible explanation could relate to the screens displaying the CS+ and CS-. Given the position of the screens parallel to the initial segment of the side arm, information from the contralateral eye would only add noise to the visual information which needs to be processed. This hypothesis, however, would not explain the sustained nature of the response. An alternative explanation holds that the deactivations are a consequence of the set-up. During a left trial, the left visual field faces towards the centre of the maze, while during a right trial the left visual field faces away from the maze to the rest of the room. The rest of the room is full of objects (distal cues) and would also be the more uncertain or dangerous part of the environment. As such it could be beneficial to prioritize processing of visual information from the right visual field during a left arm choice.

We have to be careful though not to get lost in the very bias we are addressing here. Deactivations do not have to represent decreased processing, they could also correlate with increases in sensory processing. Deactivations with respect to baseline can increase the dynamic range of neuronal responses and enhance the contrast between firing rates to different conditions.

Sustained responses in the perirhinal cortex - Are they spatial?

Above we have reviewed a large piece of PRH literature. The question remains: how do the sustained responses we have observed in chapter 4 fit with current the literature? And to address the elephant in the room: are the sustained responses spatial?

The above examples show some of the difficulties in assessing the function of higher brain areas and different pathways. Assigning functionalities to different brain areas is important to gain an overview brain function, however, we should keep in mind that these labels often originated from particular hypotheses and can become embellished over time (for instance the "what" and "where" pathways getting more and more segregated). Therefore, one should also be open to think outside the confines of the current labels. A lack of clear definitions also hurts. The lack of clear delineations of PRH borders until the late 90s for example make it much more difficult to compare older studies regarding PRH function with current ones.

Lesion studies have shown the difficulties in assessing PRH function, because the timing of the lesions, either before or after learning, can greatly alter

the effect. As a result, for at least part of the functions ascribed to the PRH, PRH appears useful but non-essential. Other areas may take over functions from PRH or they can mask deficits by providing alternative solutions as shown by studies of (Winters and Reid, 2010; Ramos, 2017). Single unit recordings show that PRH activity is generally centred around objects, but also that PRH is responsive to different actions, spatial contexts, and stimuli in a task including object-response associations.

Even though there seem to be two main pathways - one going through PRH-LEC and the other through POR-MEC - the first associated with object and the second with spatial representations - it has become clear that there is ample cross-talk between the two pathways: 1) Area 36 receives ample projections from POR; 2) POR, preferentially targets the MEC, but also has reciprocal connections with the LEC; 3) There are intrinsic connections between the LEC and MEC; 4) Cells from layer II of the LEC project to outer third of the molecular layer/stratum lacunosum moleculare of the DG and CA3, while layer II cells of the MEC project to the middle third of these layers. Thus, LEC and MEC likely terminate on dendrites of the same neurons in DG and CA3 (McNaughton and Barnes, 1977; Witter et al., 2000); 5) PRH receives direct inputs from distal CA1. Even though place fields in distal CA1 are less spatially confined than proximal CA1 place fields, they are still place fields carrying spatial information; 6) Some spatial responses have also been found in the LEC (Yoganarasimha et al., 2011; Deshmukh and Knierim, 2011; Neunuebel et al., 2013; Knierim et al., 2014; Connor and Knierim, 2017); 7) Ablating PRH reduces HPC place field stability across delays and reduces modulation of place cells by movement (Muir and Bilkey, 2001, 2003). In the latter study, the authors also show that a reduced percentage of HPC neurons showed theta phase locking. In those that did, the phase was advanced with respect to controls.

Instead of an object/space distinction an alternative hypothesis about the difference between the PRH-LEC and POR-MEC pathways is a distinction in coding for proximal versus distal frameworks, respectively (Neunuebel et al., 2013; Knierim et al., 2014). In Neunuebel et al. (2013), rats had to walk clockwise laps on a circular maze. On the maze itself, each quadrant had a different flooring pattern (local cue) and around the maze several objects were placed (distal cues). After initial exploration both the maze and the distal cues were rotated in opposite directions. The authors showed that LEC neurons preferably rotated with the local cues, while MEC neurons shifted with the distal cues. This is in line with studies investigating head direction cells in the MEC which also tend to rotate with distal cues (Yoganarasimha et al., 2006; Knight et al., 2011).

Proximal and distal landmarks are thought to provide differential information for navigation and place learning, whereby proximal cues are more important for object-place learning, while distal cues work best for spatial navigation (Benhamou and Poucet, 1998; Sanchez et al., 2016). To date no double cue rotation studies have been performed in combination with recordings in the per-

irhinal cortex. However, given the oft object-centric nature of PRH responses it is likely that PRH responses will be driven by proximal cues over distal ones.

As described above the PRH is thought to be important for attributing features of objects and adding learned associations to objects. Combining different features into a single entity (e.g. an object) is referred to as unitization (Burke et al., 2012; Kent and Brown, 2012). An important question here is how borders are determined. When should objects be combined into a single object and where does the object end and do the surroundings begin?

One way to interpret the sustained responses in the PRH (chapter 4) is by saying that they are spatial representations of the different parts of the maze. But given all previously mentioned papers PRH does not seem to be required in most spatial tasks. We could also rephrase and propose that the sustained responses are bounded by sensory features corresponding to the local spatial environment. Is this a purely semantic difference? In a simple open field or linear environment one could argue that it is, but not when one has to deal with more complex environments. With increasing complexity at some point sensory discriminants have to be used to parse the complex space into simple subsections. In this view knowledge about the task will help the rats to split the figure-8 maze into three compounded objects or segments; middle arm, left arm and right arm. This segmentation may have been facilitated by the use of doors and blocking walls.

This will raise the question where objects coding stops and when contextual coding begins. One answer is that this will happen where the subject chooses to decide to draw a line. This can depend on complexity of the objects and the surroundings, but also on task demands. What constitutes an object? One hypothesis holds that PRH will segment or unitize inside out, starting with the closest set of stimuli. In our task the only physical objects on the maze are the small ceramic cups in which the rewards are presented and the sandpaper on a part of the side-walls. Apart from those the main object, with which the rat interacts, is the maze itself plus the blocking walls. With the aid of the blocking walls, the maze is segmented in middle, left and right arms, which have different meanings in the task. In contrast, in the studies by Burke et al. (2012) and Deshmukh et al. (2012), complex objects were placed in simple environments. Here the objects are the most salient proximal features to encode. When removing the objects (Burke et al. 2012) the circular environment is so simple that it does not require segmentation. It is possible that PRH unitizes the environment into a single whole. However, without different segments to contrast PRH responses to, any sustained activity can easily be mistaken for baseline activity. Interestingly, during personal communication Burke has mentioned that they did find activations across the whole environment. Unfortunately, I can only speculate if this is indeed a similar kind of response as the sustained responses we reported in chapter 4. In contrast, Keene et al. (2016) did use an environment which is easily segmented and, importantly, in their task the environments needed to be distinguished to obtain rewards. In this study, contextual segmentation by PRH is observed in their neuronal responses.

Similar to the role of the PRH in object discrimination and fear conditioning, complexity could be a key factor. PRH is consistently recruited when task complexity is increased.

There is one more study which mentions spatial coding in the PRH and shows results which are mostly in line with what we found. Zironi et al. (2001) found spatial or location-related firing in the PRH of healthy controls and of prefrontal cortex lesioned rats. Animals were lesioned before training. They taught rats a spatial non-match to sample task in a T-maze. During the sample phase one arm of the T was blocked and the animals were forced to go e.g. left to get a reward. In the subsequent test-phase none of the arms was blocked and the animal had to go right in our example to get the reward. During the sample phase, most of the recorded PRH cells showed spatial related firing (73% for controls and 82% for PFC lesioned animals). A smaller percentage distinguished between left and right sided trials (18% for controls and 27% for PFC lesioned animals, no significant difference between groups). During the test phase there was a significant difference in left/right selectivity between control animals and PFC lesioned animals, 5% and 27% respectively.

Even though their numbers are overall lower than the percentages we found, the modulation by PFC lesions is intriguing. Why would their PFC lesioned animals show more of the location-related responses we have so abundantly found in healthy animals and how could we explain their increased prevalence in PFC lesioned animals with respect to controls? A cheap shot could be a difference in training. While Zironi et al. (2001) mention that their animals were overtrained, they do not mention training durations. Both groups were trained to a criterion of 80% after which recording started. Given the effects of PFC lesions on this type of task it would be fair to assume that the PFC lesioned group had received more training on the maze. Increased familiarity with the set-up could lead to more segmentation. Zironi et al. (2001) also describe increased firing rates in PFC lesioned animals. Given that every recording session consisted of only five leftward and five rightward trials, the increased firing rate could lead to a detection bias. Another explanation proposed by Zironi et al. (2001) holds that the increase in PRH responses is part of a compensatory mechanism to cope with PFC lesions. Patients with PFC lesions show an increased dependence on environmental cues to guide their behaviour (Lhermitte, 1983). This increased utilization of environmental cues could increase the demand on PRH related functions, including the location related signals.

In the final figure of chapter 4, Figure 5, we hint that the HPC could have an important function in the generation of the sustained responses of PRH cells. First, PRH spikes specifically locked to HPC theta. Second, units which more clearly distinguish between the left and right arms of the figure-8 maze are more strongly coupled to HPC theta, but not to beta or gamma. This coupling could indicate a way in which the HPC can provide top-down information to PRH. Top-down

information could contain spatial information which could assist in locking the extended responses PRH to locations on the maze. Lesioning PRH impairs HPC place field stability, causing shifts in place field firing across short and long delays (2 min., 1 hr., and 24 hrs.) between sessions of a simple foraging task (Muir and Bilkey, 2001). Unitized and parsed information from PRH about the environment could in turn facilitate locking hippocampal activity to the room.

In simple open field environments, it is unlikely that the animals require higher order sensory inputs to navigate the environment. It is more likely that the place field instability is caused by recognition errors; the environment is not recognized as the environment which was visited before, thereby causing place field remapping. Hargreaves et al. (2005) and Yoganarasimha et al. (2011) showed that neurons in the LEC are not spatially tuned to landmarks in cue-rich environments. When contrasted to our study it could be argued that the 'complex' open field or single pathway environments used in these studies were not behaviourally relevant or complex enough to fully engage the PRH. Alternatively, the presence of many local objects can preclude the PRH from also coding for the landmarks.

Kinnavane et al. (2014, 2015) showed that novel stimuli recruit a different pathway with respect to familiar stimuli. Novel stimuli take the 'long' way from PRH to LEC to DG/CA3 to CA1, while familiar stimuli recruit the more direct pathway from PRH to LEC to CA1. A direct return projection from CA1 to PRH (or via LEC) could facilitate recognition and navigation through a highly familiar complex environment. A feedback projection like this could assist in the fast and consistent segmentation seen in our data.

Coming back to the initial question: Are the sustained responses we observed spatial? Of course, this is a question I cannot answer yet. For now, though, I think we should see these responses as sensory representations of space, which would be a soft 'no'. PRH facilitates in segmenting more complex environments into subsections. This segmentation is guided by spatial layout and task demands. PRH is important for unitizing entities, i.e. grouping features of the maze arms, surroundings and the task into functional segments. Whether these entities have to be sensory or could also be spatial, remains to be determined.

Future perspectives

The spatially bounded responses found in chapter 4 show a new type of response for the PRH. As such there are many different follow up experiments which can be thought of to further our understanding of the described phenomena.

We propose that the spatially extended PRH responses serve a function in segmenting the environment. In order to segment a scene or environment one needs to have knowledge about the different elements making up the scene. One of the first topics to test would be the effect of familiarity on the segmentation. So far, we have only recorded animals which have been extensively trained in a visual discrimination task. As such it would be interesting to record naive animals while they familiarize themselves with an environment which is composed of dif-

ferent spatial segments. The question is if the PRH will automatically distinguish different segments in an environment (analogous to hippocampal place fields) or whether it requires a task rule, to segment a location. Previous studies have shown that PRH involvement is specifically triggered by tasks including clear reward contingencies (von Linstow Roloff et al., 2016).

If PRH is involved in segmenting the environment, PRH responses should also differentiate segments in more complex environments than a figure-8 maze. The figure-8 maze in our task was segmented into two or three parts depending on how one looks at it. Centre arm activity was defined as baseline activity and activation in the left and right arm provided deviations from this baseline. Devising an environment with more arms (like a flower shaped maze) or multiple interconnected discrete rooms could elucidate to which extent the PRH can distinguish between different parts of the environment (for instance like the complex maze used by Tanila et al. (2017).

In order to test if PRH responses will only lock to spatial context when it is not engaged by other more proximal objects, one could use the previously proposed set-up consisting of multiple chambers, but now instead of empty chambers one can place multiple objects in each chamber. In this environment PRH would be challenged with both proximal and distal complex objects. One question would entail whether the different rooms will be segmented equally well in the presence or absence of the objects.

We have argued that it is unlikely that the extended responses are a result of vestibular activity (Figure 3I in chapter 4). However, this can also be tested explicitly by using a setup in which there are either more variable paths or paths which counterbalance vestibular input. One could use a circular maze with a straight path through the middle and reward ports at each end. This setup creates three paths; two with strong rotational vestibular inputs, left and right curves and one without, the straight path. Alternatively, if we wish to stay close to our original setup we could also design a figure-8 type maze in which a left sided response not only consists of a semi-circle, but instead requires the animal to rotate left-right and left again (akin to a multiple T-maze task; Johnson and Redish, 2007), thereby inducing different vestibular inputs during the same segment.

Both previous designs testing segmentation and the effect of vestibular inputs could also be applied using virtual reality (VR) setups. Using VR, we can highly reduce variability in vestibular inputs, even though it would induce a mismatch between vestibular inputs and visual flow. Using VR would provide an advantage in segmentation in that we can use 3D environments with different levels of complexity, including paths crossing over and under each other. Even though VR allows many possibilities in task design I would prefer to test some of the above in a real-life environment first. We have found the sustained responses in 3 animals, but, being the unexpected result that it is, I would propose a replication with a smaller manipulation first to validate the robustness of the responses we have found. I have done a first pilot testing a different strain of animals in the same figure-8 maze but on a simpler task. Unfortunately, the new Tucker Davis setup that

we used for recordings could, contrary to specifications, not handle 128 channels, which induced noise to the recordings. Even though the recordings were very noisy and cannot fully be trusted, due to the random Tucker Davis induced noise artefacts, PRH units and not units recorded from other areas tended to show the characteristic responses described in chapter 4. It is nonetheless comforting to find the general pattern in a different strain, even in suboptimal recordings.

Finally, one of the most frequently asked questions by people with roots in hippocampal place field or entorhinal grid cell research is: what happens if the set-up is rotated 180 degrees? Do the firing fields remain associated with the same side-arm or do they shift? Zironi et al. (2001) report one example of a unit which first seemed to rotate with the maze. When the same animal was tested in a different maze (open field and T-maze), they showed that the firing field locked to the southern half of the room more than to the mazes itself. It is unlikely that our sustained responses solely locked to the room rather than the figure-8 maze given that we only find left-right distinctions. None of the cells were selective for the upper (containing both screens) or lower part (containing two reward wells) of the figure-8 maze. As such I would argue that based on our results the firing activity locked to the left, right, and middle arms of the setup. However, whether the fields may flip sides remains an interesting question. This question was part of the corrupted experiments where we intended to do 90 degree and 180-degree maze rotations and room cue rotations. Currently, these rotation experiments will picked up by a new PhD-student in the lab, so we should have more insight concerning this soon.

Another interesting future analysis would be to contrast the contribution of different cell types. A quick look revealed that interneurons, bursty and regular spiking putative pyramidal cells all showed differential coding for left versus right sided trials. We did not, however, look into specific firing patterns and differences in on- and offset stability. Investigating the firing patterns of different groups of neurons could increase our understanding of the nature and sustainedness of the response.

Rat Robot discussion – Keeping track of both the position of oneself and others

In the initial design of the 'Rat Robot' experiment described in chapter 5, we set out to investigate whether mirror-neuron like firing could be observed in hippocampal CA1 place field activity in relation to movements of other agents. Early 2018 two highly relevant papers were published back to back in Science. Surprisingly - whereas we did not observe any mirror-like place field activation - both of these studies did, in rats (Danjo et al., 2018), see Figure 6A-D and in bats (Omer et al., 2018), see Figure 6E-F. The biggest difference between our study and these two is the experimental design. In the Rat Robot study, we used a segmented design where the rat first explored the maze and in a later part of the task ob-

served the robot drive around in this same environment. Danjo et al. (2018) and Omer et al. (2018) on the other hand used a more interleaved design in which the demonstrator animal either went left or right and the observer animal had to mirror these movements by going to the same locations, see Figure 6A-B. Danjo et al. (2018) also used non-congruent trials in which the observer rat had to go to the other side compared to the demonstrator rat. Such an interleaved design has the benefit of saliency. There is a clearer direct interaction between the demonstrator and the observer. The interleaved design on the other hand also has a major disadvantage, especially in the task used by Danjo et al. (2018). Here the observer animal started its movements only a fraction after the demonstrator rat started moving. As a result, during a large part of each trial both animals are moving simultaneously through a shared environment, see Figure 6C. This simultaneity in movement results in a virtually insurmountable behavioural confound. It is almost impossible to disambiguate behaviours of the two different animals to ascribe neuronal firing patterns in the observer animal to movements of either the self or the other. Danjo et al. (2018) also did not include control trials during which the observer rat traversed the environment in absence of the demonstrator to acquire a baseline activation.

The research question in Danjo et al. (2018), Omer et al. (2018), and chapter 5 was: can CA1 hippocampal place fields be used to track movements of other agents in addition to the self? This question has the inherent difficulty that one is trying to find spatial correlates for the position of another agent in a brain area which is important for keeping track of the position of self. As such the position of self can be a confound in keeping track of the other. This is even more so when the movements of self and other are as highly correlated as they are in Danjo et al. (2018). A neuron could fully account for the other agent, resulting in a textbook place field when spikes of the observer are plotted with respect of the position of the other. If the behaviour of the observer and demonstrator is correlated, however, this would result in a place field for the self as well. To be able to disambiguate these responses one needs to be able to disambiguate activity of self and the other. This can be done, for example, by including recordings without the demonstrator animal. Danjo et al. (2018) used decoders to try and disambiguate responses for self and other, however they unfortunately did not try to decode the position of the other based on the position of the self. Instead they opted for the circuitous route of using the decoded position of the self (based on neural activity) to decode the position of the other. Using a double decoding approach, it is not unexpected that they found worse decoding performance for the position of the other based on the decoded self, compared to decoding directly based on the position of the other.

Despite all of these concerns it is remarkable that Danjo et al. (2018) found mirror place fields which activate at the same location for both the observer and the demonstrator. It should be noted that they only found mirror place fields for 5% of their recorded neurons. I replicated their analysis for our data, however we failed to find a single neuron with common place fields. This is mostly due to the

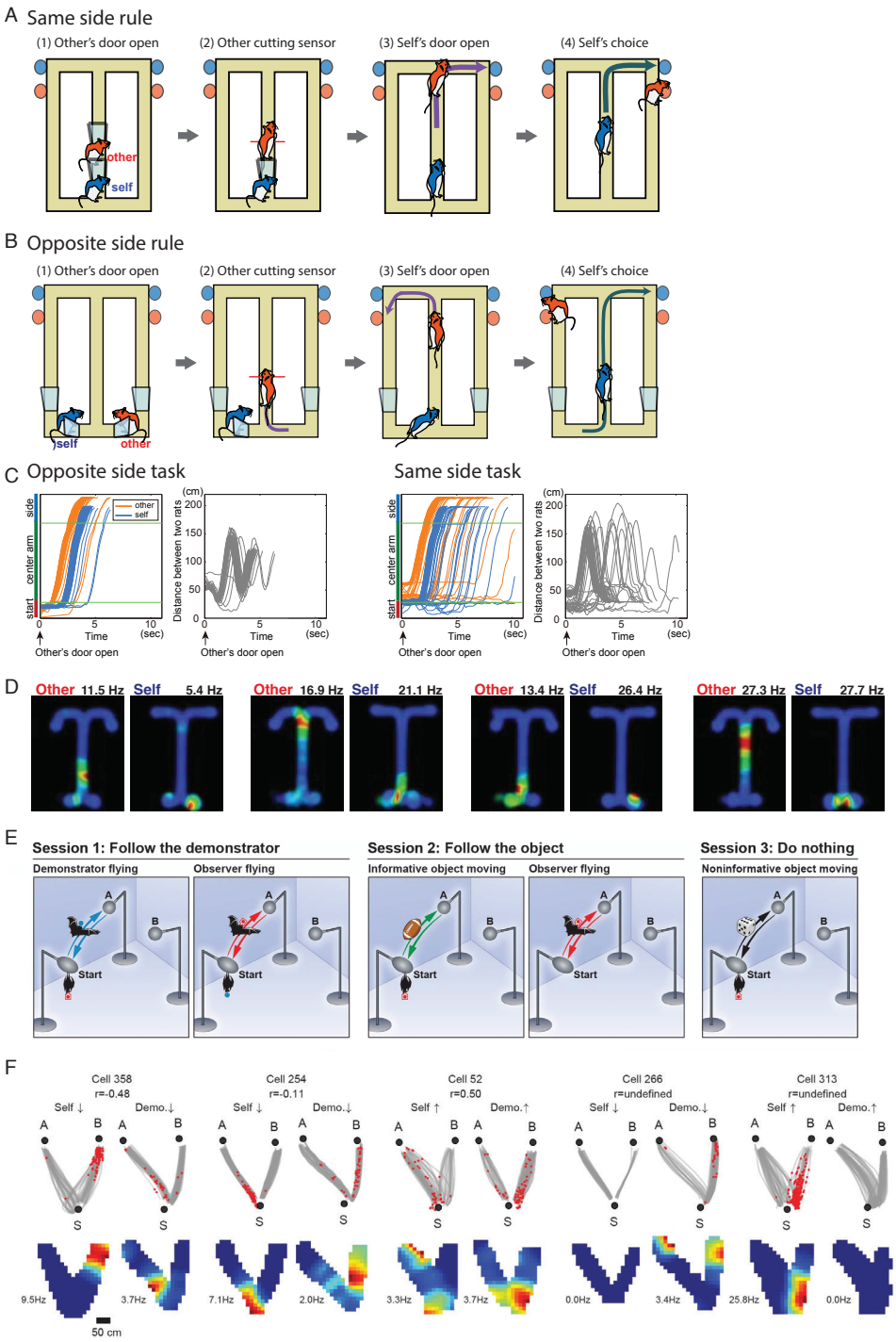

A Same side rule
(1) Other's door open
(2) Other cutting sensor
(3) Self's door open
(4) Self's choice
other
self
B Opposite side rule
(1) Other's door open
(2) Other cutting sensor
(3) Self's door open
(4) Self's choice
self
other
C Opposite side task
Same side task
side
center arm
start
other
self
Distance between two rats
(cm)
Time
(sec)
Other's door open
D
Other 11.5 Hz
Self 5.4 Hz
Other 16.9 Hz
Self 21.1 Hz
Other 13.4 Hz
Self 26.4 Hz
Other 27.3 Hz
Self 27.7 Hz
E
Session 1: Follow the demonstrator
Demonstrator flying
Observer flying
Session 2: Follow the object
Informative object moving
Observer flying
Session 3: Do nothing
Noninformative object moving
A
B
Start
F
Cell 358
r=-0.48
Cell 254
r=-0.11
Cell 52
r=0.50
Cell 266
r=undefined
Cell 313
r=undefined
Self ↓
Demo.↓
Self ↑
Demo.↑
S
9.5Hz
3.7Hz
7.1Hz
2.0Hz
3.3Hz
3.7Hz
0.0Hz
3.4Hz
25.8Hz
0.0Hz
50 cm

Figure 6 | Social place fields: representation of self and others. A-B) Two tasks used by Danjo et al. (2018). The blue rat is the observer rat (self), which was recorded, and the demonstrator rat (other) is shown in red. Each rat has their own set of reward ports denoted by blue and red circles for the observer and demonstrator, respectively. In both tasks the other rat is allowed to move first. When the other rat crossed an infrared beam in the middle arm, the door blocking the blue observer was opened. The observer rat had to either go to the same side as the demonstrator (A) or the opposite side (B). C) Movement patterns of the self (blue) and the other rat (red) for both tasks. In grey they distance between the two rats is shown. Each line depicts linearized maze routes in time for an individual trial. D) Example place fields recorded from CA1 of the hippocampus of the self, based on movement of the self or of the other. Neuronal activity is colour coded, with red depicting highest firing rates. Peak firing rates for each plot are shown on the top right. Danjo et al. (2018) show place fields for the other rat with distinct locations of activity. Additionally, values of maximum firing rates are similar for the self and the other. Images were adapted from Danjo et al. (2018). E) Behavioural paradigm used by Omer et al. (2018). The observer bat had to either follow a demonstrator bat (session 1), follow an inanimate object (session 2), or observe an inanimate object, but not follow afterwards (session 3). F) Neuronal responses recorded from CA1 of the observer bat, based on flight trajectories of the self or the demonstrator. S denotes the start locations, A and B indicate the two target locations. Grey lines show flight trajectories. Neural activity of the cells is depicted by red dots. In the bottom row of pictures, firing rates are colour coded with blue indicating minimum and red indicating maximum firing rates. Maximum firing rate is indicated at the bottom left in each plot. Similar to Danjo et al. (2018) and contrary to our results, chapter 5, Omer et al. (2018) also show succinct place fields for the demonstrator animal. In general, these firing fields did not notably overlap with the place fields of the self. Images were adapted from Omer et al. (2018).

difference in firing rates between rat and robot place fields. In our data firing rates for robot place fields were always < 50% of the firing rate of rat place fields. As such none of our units survived the restrictions of their analysis.

Omer et al. (2018) did make sure to segregate movements of the demonstrator and the observer bat, even though they also do not show a “free roaming” control (see chapter 5) where the observer bat flew in the absence of the demonstrator. Omer et al. (2018) were more cautious mentioning mirror like activity. They did find social place fields (place fields for the demonstrator), but they reported different gradations of similarity between social place fields and place fields for self, see Figure 6F. Similar to us they reported decreased firing rates for social place fields compared to place fields for self. Omer et al. (2018) performed several controls to quantify the firing behaviour in social place fields. They show that controlling for viewing angle or head movements of the observer did not significantly change firing fields. In addition to these controls, Omer et al. (2018) investigated the importance of the observer being a conspecific, changing the demonstrator rat for an object, see Figure 6E. Changing the demonstrator bat to an object decreased the similarity to self place fields (remapping) but did not decrease the information content of the spatial activity. Place fields for non-informative objects - objects which moved the same trajectory, but which were not coupled with a response from the observer animal - showed less specific activity, but they did resemble the spatial activity of informative objects more than that associated with the demonstrator rat. These results indicate that cells respond differently to objects than to conspecifics, but these different responses still carry

the same amount of information if the object was informative about the observer's upcoming movement.

Finally, an important caveat concerning Danjo et al. and Omer et al. is that they only showed their spatial results in a spatial way, viz. in the form of place fields. By showing only place fields we cannot infer the temporal stability of these responses. Are these firing fields the result of a few bursts of activity or are the responses consistent across trials? We showed the reproducibility of responses in the linearized "peri-stimulus space histogram" (PSSH, using space instead of time). Not showing the stability over trials significantly decreases the interpretability of their results.

Behaviour relevance of the demonstrator seems to be an important factor as to why Danjo et al. (2018), Omer et al. (2018) and we have found place field modulations, while previous studies have reported no or only very little modulations. Mou and Ji (2016) had rats walk on a linear maze before they were placed in an observation compartment where they observed other rats or toys cars move back and forth on the linear track. Observing the other move on the linear track increased reactivation of sequences present while on the maze, but they did not find any spatially specific firing for the other.

Similarly, introducing a second animal (von Heimendahl et al., 2012; Zynyuk et al., 2012) to a foraging rat had only minor effects on firing activity. In this set-up the second animal did not change any task rules. As such it appears that the presence of another animal without explicit rules associated with the presence of that animal only results in minor short-term effects on place field firing. Results by Ho et al. (2008) support this idea. They introduced a toy car to a rat in an open field arena. They tested animals on two tasks: the rat received intra-cranial stimulation as a reward when it moved within 20 cm of the car or the rat was rewarded if it travelled 150 cm irrespective of the position of the car. Firing rate modulations due to movement variables of the car were larger in the first condition than in the second.

All these studies show the difficulty of designing an experiment which can show the role of hippocampal CA1 neurons in tracking others. Results by Danjo et al. (2018) and Omer et al. (2018) show the benefit of a design which includes a close interaction between the observer and the demonstrator. However, care should be taken to make sure that the movements of the other and self can be disambiguated. One way this could be accomplished would be by using different spatial compartments where the observer could wait while the other moves. Additionally, this disambiguation should involve a baseline recording without the demonstrator present.

Finally, one should take care that analyses include measures which directly control for movements of the observer animal. This can be done by recording head movements or using analyses like conditional mutual information which calculates information about the other agent while correcting for the positions of

the observer. In chapter 5 we also included decoding measures which directly use the x/y coordinates of the observer to decode the task condition. Decoding using this control variable was surprisingly accurate. In all of our contrasts, except front versus mid task, accuracy for decoding task condition was higher when using position data than using neural data. This shows the risk of stereotyped behaviour of the observer animal throughout the task and serves as a clear warning that one should control for the behaviour of the observer as well.

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